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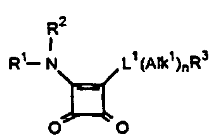
(54) Title: SQUARIC ACID DERIVATIVES AS INTEGRIN ANTAGONISTS



(1) $-CH_2-CH(R)-$, $-CH=C(R)-$, $-\underset{CH_2R}{\underset{|}{CH}}-$ (a)

(57) Abstract: Squaric acid derivatives of formula (1) are described wherein R^1 is a group Ar^1Ar^2Alk- in which Ar^1 is an optionally substituted aromatic or heteroaromatic group; Ar^2 is an optionally substituted phenylene or nitrogen-containing six-membered heteroarylene group; and Alk is a chain $-CH_2-CH(R)-$, $CH=C=C(R)-$, (a) in which R is a carboxylic acid ($-CO_2H$) or a derivative or biostere thereof; R^2 is a hydrogen atom or a C_{1-6}alkyl group; L^1 is a covalent bond or a linker atom or group; n is zero or the integer 1; Alk^1 is an optionally substituted aliphatic chain; R^3 is a hydrogen atom or an optionally substituted heteroaliphatic, cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, heteropolycycloaliphatic, aromatic or heteroaromatic group: and the salts, solvates, hydrates and N-oxides thereof. The compounds are able to inhibit the binding of integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders, or disorders involving the inappropriate growth or migration of cells.

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SQUARIC ACID DERIVATIVES AS INTEGRIN ANTAGONISTS

This invention relates to a series of biaryl squaric acid derivatives, to compositions containing them, to processes for their preparation, and to their use in medicine.

Over the last few years it has become increasingly clear that the physical interaction of inflammatory leukocytes with each other and other cells of the body plays an important role in regulating immune and inflammatory responses [Springer, T. A., Nature, 346, 425, (1990); Springer, T. A., Cell, 76, 301, (1994)]. Specific cell surface molecules collectively referred to as cell adhesion molecules mediate many of these interactions.

The adhesion molecules have been sub-divided into different groups on the basis of their structure. One family of adhesion molecules which is believed to play a particularly important role in regulating immune and inflammatory responses is the integrin family. This family of cell surface glycoproteins has a typical non-covalently linked heterodimer structure. At least 16 different integrin alpha chains and 8 different integrin beta chains have been identified [Newman, P. *et al*, Molecular Medicine Today, 304, (1996)]. The members of the family are typically named according to their heterodimer composition although trivial nomenclature is widespread in the field. Thus the integrin $\alpha4\beta1$ consists of the integrin alpha 4 chain associated with the integrin beta 1 chain, but is also widely referred to as Very Late Antigen 4 or VLA-4. Not all of the potential pairings of integrin alpha and beta chains have yet been observed in nature and the integrin family has been subdivided into a number of subgroups based on the pairings that have been recognised to date [Sonnenberg, A., Current Topics in Microbiology and Immunology, 184, 7, (1993)].

The importance of integrin function in normal physiological responses is highlighted by two human deficiency diseases in which integrin function is d fective. Thus in the disease term d Leukocyt Adhesion Deficiency (LAD) there is a defect in one of the families of integrins expressed on leukocytes [Marlin, S. D. *et al*, J. Exp. Med. 164, 855, (1986)]. Patients

suffering from this disease have a reduced ability to recruit leukocytes to inflammatory sites and suffer recurrent infections, which in extreme cases may be fatal. In the case of patients suffering from the disease termed Glanzman's thrombasthenia (a defect in a member of the beta 3 integrin family) there is a defect in blood clotting (Hodivala-Dilke, K. M., J. Clin. Invest. 103, 229, (1999)].

The potential to modify integrin function in such a way as to beneficially modulate cell adhesion has been extensively investigated in animal models using specific antibodies and peptides that block various functions of these molecules [e.g. Issekutz, T. B., J. Immunol. 149, 3394, (1992); Li, Z. *et al*, Am. J. Physiol. 263, L723, (1992); Mitjans, F. *et al*, J. Cell Sci. 108, 2825, (1995); Brooks, P. C. *et al*, J. Clin. Invest. 96, 1815, (1995); Binns, R. M. *et al*, J. Immunol. 157, 4094, (1996); Hammes, H.-P. *et al*, Nature Medicine 2, 529, (1996); Srivata, S. *et al*, Cardiovascular Res. 36, 408 (1997)]. A number of monoclonal antibodies which block integrin function are currently being investigated for their therapeutic potential in human disease, and one, ReoPro, a chimeric antibody against the platelet integrin αIIbβ3 is in use as a potent anti-thrombotic agent for use in patients with cardiovascular complications following coronary angioplasty.

Integrins recognize both cell surface and extracellular matrix ligands, and ligand specificity is determined by the particular alpha-beta subunit combination of the molecule [Newman, P., *ibid*]. One particular integrin subgroup of interest involves the α4 chain which can pair with two different beta chains β1 and β7 [Sonnenberg, A., *ibid*]. The α4β1 pairing occurs on many circulating leukocytes (for example lymphocytes, monocytes, eosinophils and basophils) although it is absent or only present at low levels on circulating neutrophils. α4β1 binds to an adhesion molecule (Vascular Cell Adhesion Molecule-1 also known as VCAM-1) frequently up-regulated on endothelial cells at sites of inflammation [Osborne, L., Cell, 62, 3, (1990)]. The molecule has also been shown to bind to at least three sites in the matrix molecule fibronectin [Humphries, M. J. *et al*, Ciba Foundation Symposium, 189, 177, (1995)]. Based on data obtained with monoclonal antibodies in animal models it is believed that the interaction b tw en α4β1 and ligands on other cells and the extracellular matrix plays

an important role in leukocyte migration and activation [Yednock, T. A. *et al*, Nature, 356, 63, (1992); Podolsky, D. K. *et al*, J. Clin. Invest. 92, 372, (1993); Abraham, W. M. *et al*, J. Clin. Invest. 93, 776, (1994)].

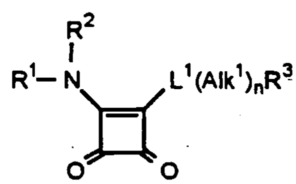
The integrin generated by the pairing of $\alpha 4$ and $\beta 7$ has been termed LPAM-1 [Holzmann, B. and Weissman, I. L., EMBO J. 8, 1735, (1989)]. The $\alpha 4\beta 7$ pairing is expressed on certain sub-populations of T and B lymphocytes and on eosinophils [Erle, D. J. *et al*, J. Immunol. 153, 517 (1994)]. Like $\alpha 4\beta 1$, $\alpha 4\beta 7$ binds to VCAM-1 and fibronectin. In addition, $\alpha 4\beta 7$ binds to an adhesion molecule believed to be involved in the homing of leukocytes to mucosal tissue termed MAdCAM-1 [Berlin, C. *et al*, Cell, 74, 185, (1993)]. The interaction between $\alpha 4\beta 7$ and MAdCAM-1 may also be important sites of inflammation outside of mucosal tissue [Yang, X.-D. *et al*, PNAS, 91, 12604, (1994)].

Regions of the peptide sequence recognizeded by $\alpha 4\beta 1$ and $\alpha 4\beta 7$ when they bind to their ligands have been identified. $\alpha 4\beta 1$ seems to recognise LDV, IDA or REDV peptide sequences in fibronectin and a QIDSP sequence in VCAM-1 [Humphries, M. J. *et al*, *ibid*] whilst $\alpha 4\beta 7$ recognises a LDT sequence in MAdCAM-1 [Birskin, M. J. *et al*, J. Immunol. 156, 719, (1996)]. There have been several reports of inhibitors of these interactions being designed from modifications of these short peptide sequences [Cardarelli, P. M. *et al*, J. Biol. Chem., 269, 18668, (1994); Shorff, H. N. *et al*, Biorganic Med. Chem. Lett., 6, 2495, (1996); Vanderslice, P. *et al*, J. Immunol., 158, 1710, (1997)]. It has also been reported that a short peptide sequence derived from the $\alpha 4\beta 1$ binding site in fibronectin can inhibit a contact hypersensitivity reaction in a trinitrochlorobenzene sensitised mouse [Ferguson, T. A., *et al*, PNAS, 88, 8072, (1991)].

Since the alpha 4 subgroup of integrins are predominantly expressed on leukocytes their inhibition can be expected to be beneficial in a number of immune or inflammatory disease states. However, because of the ubiquitous distribution and wide range of functions performed by other memb rs of the integrin family it is important to be able to identify selectiv inhibitors of the alpha 4 subgroup.

We have now found a group of compounds which are potent and selective inhibitors of $\alpha 4$ integrins. Members of the group are able to inhibit $\alpha 4$ integrins such as $\alpha 4\beta 1$ and/or $\alpha 4\beta 7$ at concentrations at which they generally have no or minimal inhibitory action on α integrins of other subgroups. These compounds possess the additional advantage of good pharmacokinetic properties, especially low plasma clearance.

Thus according to one aspect of the invention we provide a compound of formula (1)



(1)

wherein

R^1 is a group Ar^1Ar^2Alk- in which:

Ar^1 is an optionally substituted aromatic or heteroaromatic group;

Ar^2 is an optionally substituted phenylene or nitrogen-containing six-membered heteroarylene group; and Alk is a chain

$-CH_2-CH(R)-$, $-CH=C(R)-$, $\underset{\displaystyle CH_2R}{\overset{|}{-CH-}}$

in which R is a carboxylic acid ($-CO_2H$) or a derivative or biostere thereof;

R^2 is a hydrogen atom or a C_{1-6}alkyl group;

L^1 is a covalent bond or a linker atom or group;

n is zero or the integer 1;

Alk^1 is an optionally substituted aliphatic chain;

R^3 is a hydrogen atom or an optionally substituted heteroaliphatic, cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, heteropolycycloaliphatic, aromatic or heteroaromatic group:

and the salts, solvates, hydrates and N-oxides thereof.

It will be appreciated that compounds of formula (1) may have one or more chiral centres, and exist as enantiom rs or diastereomers. The invention is

to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (1) may exist as tautomers, for example keto ($CH_2C{=}O$)-enol ($CH{=}CHOH$) tautomers. Formula (1) and the formulae hereinafter are intended to represent all individual tautomers and mixtures thereof, unless stated otherwise.

Optionally substituted aromatic groups represented by Ar^1 when present in the group R^1 include for example optionally substituted monocyclic or bicyclic fused ring C_{6-12} aromatic groups, such as phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups.

Optionally substituted heteroaromatic groups represented by the group Ar^1 when present in the group R^1 include for example optionally substituted C_{1-9} heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include pyrrolyl, furyl, thienyl, imidazolyl, N-C_{1-6}alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, isobenzofuryl, [2,3-dihydro]benzofuryl, [2,3-dihydro]benzothienyl, benzothienyl, benzotriazolyl, indolyl, indolinyl, isoindolyl, indazolinyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzoisoxazolyl, benzopyranyl,

[3,4-dihydro]benzopyranyl, benzofurazonyl, quinazolinyl, purinyl, quinoxalinyl, naphthyridinyl, especially 2,6-naphthyridinyl, pyrido[3,4-b]pyridyl, phthalazinyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]-pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Each aromatic or heteroaromatic group represented by the group Ar^1 may be optionally substituted on any available carbon or, when present, nitrogen atom. One, two, three or more of the same or different substituents may be present and each substituent may be selected for example from an atom or group $-L^2(Alk^2)_tL^3(R^4)_u$ in which L^2 and L^3 which may be the same or different, is each a covalent bond or a linker atom or group, t is zero or the integer 1, u is an integer 1, 2 or 3, Alk^2 is an aliphatic or heteroaliphatic chain and R^4 is a hydrogen or halogen atom or a group selected from optionally substituted C_{1-6}alkyl or C_{3-8}cycloalkyl, -Het, [where Het is an optionally substituted monocyclic C_{5-7}carbocyclic group optionally containing one or more -O- or -S- atoms or $-N(R^5)-$ (where R^5 is a hydrogen atom or an optionally substitued C_{1-6}alkyl or C_{3-8}cycloalkyl group), -C(O)- or -C(S)- groups], $-OR^5$ $-SR^5$, $-NR^5R^6$ [where R^6 is as just defined for R^5 and may be the same or different], $-NO_2$, -CN, $-CO_2R^5$, $-SO_3H$, $-SOR^5$, $-SO_2R^5$, $-SO_3R^5$, $-OCO_2R^5$, $-CONR^5R^6$, $-OCONR^5R^6$, $-CSNR^5R^6$, $-COR^5$, $-OCOR^5$, $-N(R^5)COR^6$, $-N(R^5)CSR^6$, $-SO_2N(R^5)(R^6)$, $-N(R^5)SO_2R^6$, $-CON(R^5)SO_2R^6$, $-N(R^5)CON(R^6)(R^7)$ [where R^7 is a hydrogen atom or an optionally substituted C_{1-6}alkyl or C_{3-8}cycloalkyl group], $-N(R^5)CSN(R^6)(R^7)$ or $-N(R^5)SO_2N(R^6)(R^7)$, provided that when t is zero and each of L^2 and L^3 is a covalent bond then u is the integer 1 and R^4 is other than a hydrogen atom

When L^2 and/or L^3 is present in these substituents as a linker atom or group it may be any divalent linking atom or group. Particular examples include -O- or -S- atoms or -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^8)-$ [where R^8 is a hydrogen atom or an optionally substitut d C_{1-6}alkyl group], $-CON(R^8)-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)CON(R^8)-$, $-N(R^8)CSN(R^8)-$, or $-N(R^8)SO_2N(R^8)-$ groups. Where

the linker group contains two R^8 substituents, these may be the same or different.

When R^4, R^5, R^6, R^7 and/or R^8 is present as a C_{1-6}alkyl group it may be a straight or branched C_{1-6}alkyl group, e.g. a C_{1-4}alkyl group such as a methyl, ethyl, i-propyl or t-butyl group. C_{3-8}cycloalkyl groups represented by R^4, R^5, R^6, R^7 and/or R^8 include C_{3-6}cycloalkyl groups e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. Optional substituents which may be present on such groups include for example one, two or three substituents which may be the same or different selected from halogen atoms, for example fluorine, chlorine, bromine or iodine atoms, hydroxy or C_{1-6}alkoxy e.g. methoxy or ethoxy groups or optionally substituted C_{6-12}aryl or optionally substituted C_{1-9}heteroaryl. Optionally substituted aryl and heteroaryl groups include those groups just described for the group Ar^1.

When the groups R^5 and R^6 or R^6 and R^7 are both C_{1-6}alkyl groups these groups may be joined, together with the N atom to which they are attached, to form a heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a further heteroatom selected from -O-, -S- or $-N(R^5)-$. Particular examples of such heterocyclic rings include piperidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl and piperazinyl rings.

When Alk^2 is present as an aliphatic or heteroaliphatic chain it may be for example any divalent chain corresponding to the below-mentioned aliphatic or heteroaliphatic group described for Alk^1 or R^3 respectively.

Halogen atoms represented by R^4 in the optional Ar^1 substituents include fluorine, chlorine, bromine, or iodine atoms.

Examples of the substituents represented by $-L^2(Alk^2)_tL^3(R^4)_u$ when present in Ar^1 groups in compounds of the invention include atoms or groups $-L^2Alk^2L^3R^4$, $-L^2Alk^2R^4$, $-L^2R^4$ and $-Alk^2R^4$ wherein L^2, Alk^2, L^3 and R^4 are as d fined above. Particular examples of such substituents include $-L^2CH_2L^3R^4$, $-L^2CH(CH_3)L^3R^4$, $-L^2CH(CH_2)_3L^3R^4$, $-L^2CH_2R^4$,

$-L^2CH(CH_3)R^4$, $-L^2(CH_2)_2R^4$, $-CH_2R^4$, $-CH(CH_3)R^4$, $-(CH_2)_2R^4$ and $-R^4$ groups.

Thus Ar^1 in compounds of the invention may be optionally substituted for example by one, two, three or more halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, and/or C_{1-6}alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, C_{3-8}cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl or $-C(OH)(CF_3)_2$, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, oxazolidinyl, carboxyC_{1-6}alkyl, e.g. carboxyethyl, C_{1-6}alkylthio e.g. methylthio or ethylthio, carboxyC_{1-6}alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C_{1-6}alkoxy, e.g. methoxy or ethoxy, hydroxyC_{1-6}alkoxy, e.g. 2-hydroxyethoxy, haloC_{1-6}alkyl, e.g. $-CF_3$, $-CHF_2$, $-CH_2F$, haloC_{1-6}alkoxy, e.g. $-OCF_3$, $-OCHF_2$, $-OCH_2F$, C_{1-6}alkylamino, e.g. methylamino or ethylamino, amino ($-NH_2$), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, C_{1-6}alkylaminoC_{1-6}alkyl, e.g. ethylaminoethyl, C_{1-6} dialkylaminoC_{1-6}alkyl, e.g. diethylaminoethyl, aminoC_{1-6}alkylamino e.g. aminoethylamino, aminoC_{1-6}alkoxy, e.g. aminoethoxy, hydroxyC_{1-6}alkylamino e.g. hydroxyethylamino or hydroxyropylamino, C_{1-6}alkylaminoC_{1-6}alkoxy, e.g. methylaminoethoxy, C_{1-6}dialkylaminoC_{1-6}alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl ($-CO_2H$), $-CO_2Alk^3$ [where Alk^3 is as defined below for Alk^7], C_{1-6} alkanoyl e.g. acetyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, sulphonyl ($-SO_3H$), $-SO_3Alk^3$, C_{1-6}alkylsulphinyl e.g. methylsulphinyl, ethylsulphinyl or propylsulphinyl, C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6} alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido ($-CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6}dialkylaminocarbonyl, .g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC_{1-6}alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C_{1-6}dialkylaminoC_{1-6}alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonyl-

amino, C_{1-6}alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C_{1-6}dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C_{1-6}alkylaminocarbonylC_{1-6}alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C_{1-6}dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylC_{1-6}alkylamino, e.g. ethylaminothiocarbonylmethylamino, C_{1-6}alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C_{1-6}dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, aminosulphonylamino ($-NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, aminoC_{1-6}alkanoylamino e.g. aminoacetylamino, C_{1-6}dialkylaminoC_{1-6}alkanoylamino, e.g. dimethylaminoacetylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, C_{1-6}alkanoylaminoC_{1-6}alkylamino, e.g. acetamidoethylamino, C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino groups.

Where desired, two $-L^2(Alk^2)_tL^3(R^4)_u$ substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6}alkylenedioxy group such as methylenedioxy or ethylenedioxy.

Optionally substituted nitrogen-containing six-membered heteroarylene groups represented by Ar^2 when present as part of the group R^1 include optionally substituted pyridiyl, pyrimidindiyl, pyridazindiyl, pyrazindiyl and triazindiyl e.g. 1,2,4-triazindiyl groups. Each group may be attached to the remainder of the molecule through any available ring carbon atoms.

The phenylene and nitrogen-containing heteroarylene groups represented by Ar^2 may be optionally substituted by one or two substituents selected from the atoms or groups $-L^3(Alk^2)_tL^3(R^4)_u$ described herein. Where two of these atoms or groups are present they may be the same or different.

When the group R is present in R^1 in compounds of the invention as a derivative of a carboxylic acid it may be for example a carboxylic acid ester or amide. Particular esters and amides include $-CO_2Alk^7$ and $-CONR^5R^6$ groups as defined herein. When R is a biostere of a carboxylic acid it may be for example a tetrazole or other acid such as phosphonic acid, phosphinic acid, sulphonic acid, sulphinic acid or boronic acid or an acylsulphonamide group.

Ester ($-CO_2Alk^7$) and amide ($-CONR^5R^6$) derivatives of the carboxylic acid group ($-CO_2H$) in compounds of formula (1) may advantageously be used as prodrugs of the active compound. Such prodrugs are compounds which undergo biotransformation to the corresponding carboxylic acid prior to exhibiting their pharmacological effects and the invention particularly extends to prodrugs of the acids of formula (1). Such prodrugs are well known in the art, see for example International Patent Application No. WO00/23419, Bodor, N. (Alfred Benzon Symposium, 1982, 17, 156-177), Singh, G. et al (J. Sci. Ind. Res., 1996, 55, 497-510) and Bundgaard, H., (Design of Prodrugs, 1985, Elsevier, Amsterdam).

Esterified carboxyl groups represented by the group $-CO_2Alk^7$ include those wherein Alk^7 is a straight or branched optionally substituted C_{1-8}alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; an optionally substituted C_{2-8}alkenyl group such as a propenyl e.g. 2-propenyl or butenyl e.g. 2-butenyl or 3-butenyl group, an optionally substituted C_{2-8}alkynyl group such as a ethynyl, propynyl e.g. 2-propynyl or butynyl e.g. 2-butynyl or 3-butynyl group, an optionally substituted C_{3-8}cycloalkyl group such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl group; an optionally substituted C_{3-8}cycloalkylC1-8alkyl group such as a cyclopentylmethyl, cyclohexylmethyl or cyclohexylethyl group; an optionally substituted C_{3-8}heterocycloalkylC_{1-6}alkyl group such as a morpholinyl-N-ethyl, thiomorpholinyl-N-methyl, pyrrolidinyl-N-ethyl, pyrrolidinyl-N-propyl, piperidinyl-N-ethyl, pyrazolidinyl-N-methyl or piperazinyl-N-ethyl group; an optionally substituted C_{1-6}alkyloxyC_{1-6}alkyl group such as a methyloxyethyl or propyloxyethyl group; an optionally substituted C_{1-6}alkylthioC_{1-6}alkyl group such as an ethylthioethyl group; an optionally substituted C_{1-6}alkylsulfinylC_{1-6}alkyl

group such as an methylsulfinylethyl group; an optionally substituted C_{1-6}alkylsulfonylC_{1-6}alkyl group such as an methylsulfonylmethyl group; an optionally substituted C_{3-8}cycloalkyloxyC_{1-6}alkyl group such as a cyclohexyloxymethyl group; an optionally substituted C_{3-8}cycloalkylthioC1-6alkyl group such as a cyclopentylthiomethyl group; an optionally substituted C_{3-8}cycloalkylsulfinylC_{1-6}alkyl group such as a cyclopentylsulfinylmethyl group; an optionally substituted C_{3-8}cyclo-alkylsulfonylC_{1-6}alkyl group such as a cyclopentylsulfonylmethyl group; an optionally substituted C_{1-6}alkyloxycarbonylC_{1-6}alkyl group such as isobutoxycarbonylpropyl group; an optionally substituted C_{1-6}alkyloxycarbonylC_{1-6}alkenyl group such as isobutoxycarbonylpentenyl group; an optionally substituted C_{1-6}alkyloxycarbonyloxyC_{1-6}alkyl group such as an isopropoxycarbonyloxyethyl e.g a 1-(isopropoxycarbonyloxy)-ethyl, 2-(isopropoxycarbonyloxy)ethyl or ethyloxycarbonyloxymethyl group; an optionally substituted C_{1-6}alkyloxycarbonyloxyC_{1-6}alkenyl group such as a isopropoxycarbonyloxybutenyl group, an optionally substituted C_{3-8}cycloalkyloxycarbonyloxyC_{1-6}alkyl group such as a cyclohexyloxy-carbonyloxyethyl, e.g. a 2-(cyclohexyloxycarbonyloxy)ethyl group, an optionally substituted N-di-C_{1-8}alkylaminoC_{1-8}alkyl group such as a N-dimethylaminoethyl or N-diethylaminoethyl group; an optionally substituted N-C_{6-12}aryl-N-C_{1-6}alkylaminoC_{1-6}alkyl group such as a N-phenyl-N-methylaminomethyl group; an optionally substituted N-di-C_{1-8}alkylcarbamoylC_{1-8}alkyl group such as a N-diethylcarbamoylmethyl group; an optionally substituted C_{6-10}arylC_{1-6}alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-10}aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-10}aryloxyC_{1-8}alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; a C_{6-12}arylthioC_{1-8}alkyl group such as an optionally substituted phenylthioethyl group; a C_{6-12}arylsulfinylC_{1-8}alkyl group such as an optionally substituted phenyl-sulfinylmethyl group; a C_{6-12}arylsulfonylC_{1-8}alkyl group such as an optionally substituted phenylsulfonylmethyl group; an optionally substituted C_{1-8}alkanoyloxyC_{1-8}alkyl group, such as a ac toxymethyl, ethoxycarbonyloxyethyl, pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; an optionally substituted C_{4-8}imidoC_{1-8}alkyl

group such as a succinimidomethyl or phthalamidoethyl group; a C_{6-12}aroyloxyC_{1-8}alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group or a triglyceride such as a 2-substituted triglyceride e.g. a 1,3-di-C_{1-8}alkylglycerol-2-yl group such as a 1,3-diheptylglycerol-2-yl group. Optional substituents present on the Alk^7 group include R^{13a} substituents described above.

It will be appreciated that in the forgoing list of Alk^7 groups the point of attachment to the remainder of the compound of formula (1) is via the last described part of the Alk^7 group. Thus, for example a methoxyethyl group would be attached by the ethyl group, whilst a morpholinyl-N-ethyl group would be attached via the N-ethyl group.

It will be further appreciated that in the forgoing list of Alk^7 groups, where not specifically mentioned, alkyl groups may be replaced by alkenyl or alkynyl groups where such groups are as previously defined for Alk^1. Additionally these alkyl, alkenyl or alkynyl groups may optionally be interrupted by one, two or three linker atoms or groups where such linker atoms and groups are as previously defined for L^2.

When the group R^2 is present in compounds of the invention as a C_{1-6}alkyl group it may be for example a straight or branched C_{1-6}alkyl group, e.g. a C_{1-4}alkyl group such as a methyl or ethyl group.

The linker atom or group represented by L^1 in compounds of formula (1) may be any linker atom or group as described above for the linker atom or group L^2 or may represent a covalent bond.

When the group Alk^1 is present in compounds of formula (1) as an optionally substituted aliphatic chain it may be an optionally substituted C_{1-10} aliphatic chain. Particular examples include optionally substituted straight or branched chain C_{1-6} alkylene, C_{2-6} alkenylene, or C_{2-6} alkynylene chains.

Particular examples of aliphatic chains represented by Alk^1 include optionally substituted $-CH_2-$, $-(CH_2)_2-$, $-CH(CH_3)CH_2-$, $-(CH_2)_2CH_2-$,

$-(CH_2)_3CH_2-$, $-CH(CH_3)(CH_2)_2-$, $-CH_2CH(CH_3)CH_2-$, $-C(CH_3)_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$, $-(CH_2)_2CH(CH_3)CH_2-$, $-CH(CH_3)(CH_2)_3-$, $-CH(CH_3)CH_2CH(CH_3)CH_2-$, $-CH_2CH(CH_3)CH_2CH_2-$, $-(CH_2)_2C(CH_3)_2CH_2-$, $-(CH_2)_4CH_2-$, $-(CH_2)_5CH_2-$, $-CHCH-$, $-CHCHCH_2-$, $-CH_2CHCH-$, $-CHCHCH_2CH_2-$, $-CH_2CHCHCH_2-$, $-(CH_2)_2CHCH-$, $-CC-$, $-CCCH_2-$, $-CH_2CC-$, $-CCCH_2CH_2-$, $-CH_2CCCH_2-$ or $-(CH_2)_2CCH-$ groups.

Heteroaliphatic groups represented by the group R^3 in the compounds of formula (1) include the aliphatic chains just described for Alk^1 but with each containing a terminal hydrogen atom and additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^4 where L^4 is as defined above for L^2 when L^2 is a linker atom or group. Each L^4 atom or group may interrupt the aliphatic group, or may be positioned at its terminal carbon atom to connect the group to an adjoining atom or group. Particular examples include optionally substituted $-L^4CH_3$, $-CH_2L^4CH_3$, $-L^4CH_2CH_3$, $-CH_2L^4CH_2CH_3$, $-(CH_2)_2L^4CH_3$, $-(CH_2)_3L^4CH_3$, $-L^4(CH_2)_2CH_3$ and $-(CH_2)_2L^4CH_2CH_3$ groups.

The optional substituents which may be present on aliphatic or heteroaliphatic chains represented by Alk^1 and R^3 respectively include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or -OH, -CN, $-CO_2H$, $-CO_2R^9$ [where R^9 is an optionally substituted straight or branched C_{1-6}alkyl group as defined above for R^4], $-CONHR^9$, $-CON(R^9)_2$, $-COR^9$, C_{1-6}alkoxy, e.g. methoxy or ethoxy, thiol, $-S(O)R^9$, $-S(O)_2R^9$, C_{1-6}alkylthio e.g. methylthio or ethylthio, amino or substituted amino groups or optionally substituted C_{6-12}aryl e.g. phenyl or C_{1-9}heteroaryl e.g. pyridyl. Substituted amino groups include $-NHR^9$ and $-N(R^9)_2$ groups . Where two R^9 groups are present in any of the above substituents these may be the same or different.

Optionally substituted cycloaliphatic groups represented by the group R^3 in compounds of the invention include optionally substituted C_{3-10} cycloaliphatic groups. Particular examples include optionally substituted

C_{3-10} cycloalkyl, e.g. C_{3-7} cycloalkyl or C_{3-10} cycloalkenyl, e.g C_{3-7} cycloalkenyl groups.

Optionally substituted heterocycloaliphatic groups represented by the group R^3 include optionally substituted C_{3-10}heterocycloaliphatic groups. Particular examples include optionally substituted C_{3-10}heterocycloalkyl, e.g. C_{3-7} heterocycloalkyl, or C_{3-10}heterocycloalkenyl, e.g. C_{3-7} hetercycloalkenyl groups, each of said groups containing one, two, three or four heteroatoms or heteroatom-containing groups L^4 as defined above.

Optionally substituted polycycloaliphatic groups represented by the group R^3 include optionally substitued C_{7-10} bi- or tricycloalkyl or C_{7-10}bi- or tricycloalkenyl groups. Optionally substituted heteropolycycloaliphatic groups represented by the group R^3 include the optionally substituted polycycloalkyl groups just described, but with each group additionally containing one, two, three or four L^4 atoms or groups.

Particular examples of cycloaliphatic, polycycloaliphatic, heterocyclo-aliphatic and heteropolycycloaliphatic groups represented by the group R^3 include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, adamantyl, norbornyl, norbornenyl, tetrahydrofuranyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, thiazolinyl, thiazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, homopiperidinyl, heptamethyleneiminyl, piperidinone, 1,4-dioxanyl, morpholinyl, morpholinone, 1,4-dithianyl, thiomorpholinyl, piperazinyl, homopiperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5,-oxadiazinyl groups.

The optional substituents which may be present on the cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or heterpolyocycloaliphatic groups represented by the group R^3 include one, two, three or more substituents

each selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl or ethyl, haloC_{1-6}alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, optionally substituted by hydroxyl, e.g. $-C(OH)(CF_3)_2$, C_{1-6}alkoxy, e.g. methoxy or ethoxy, haloC_{1-6}alkoxy, e.g. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, $-C_{1-6}$alkoxyC_{1-6}alkyl e.g. methoxyethyl-, C_{1-6}alkylthio e.g. methylthio or ethylthio, or $-(Alk^4)_vR^{10}$ groups in which Alk^4 is a straight or branched C_{1-3}alkylene chain, v is zero or an integer 1 and R^{10} is a -OH, -SH, $-N(R^{11})_2$ (in which R^{11} is an atom or group as defined herein for R^8) -CN, $-CO_2R^{11}$, $-NO_2$, $-CON(R^{11})_2$, $-CSN(R^{11})_2$, $-COR^{11}$, $-CSN(R^{11})_2$, $-N(R^{11})COR^{11}$, $-N(R^{11})CSR^{11}$, $-SO_2N(R^{11})_2$, $-N(R^{11})SO_2R^{11}$, $-N(R^{11})CON(R^{11})_2$, $-N(R^{11})CSN(R^{11})$, $N(R^{11})SO_2N(R^{11})_2$, $-SOR^{11}$, $-SO_2R^{11}$, $-SO_3R^{11}$ or an optionally substituted aromatic or heteroaromatic group. Where two R^{11} atoms or groups are present in these substituents these may be the same or different.

Particular examples of Alk^4 chains include $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ and $-CH(CH_3)CH_2-$ chains.

Additionally, when the group R^3 is a heterocycloaliphatic group containing one or more nitrogen atoms each nitrogen atom may be optionally substituted by a group $-(L^5)_p(Alk^5)_qR^{12}$ in which L^5 is -C(O)-, -C(O)O-, -C(S)-, $-S(O)_2-$, $-CON(R^{11})-$, $-CSN(R^{11})-$ or $SO_2N(R^{11})-$; p is zero or an integer 1; Alk^5 is an optionally substituted aliphatic or heteroaliphatic chain; q is zero or the integer 1; and R^{12} is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, heteropolycycloaliphatic, aromatic or heteroaromatic group.

Optionally substituted aliphatic or heteroaliphatic chains represented by Alk^5 include those optionally substituted chains described above for Alk^1 and R^3 respectively.

Cycloaliphatic, heterocycloaliphatic, polycycloaliphatic or polyheterocyclo-aliphatic groups represented by R^{12} include those groups just described for the group R^3. Optional substituents which may b present on these

groups include those described above in relation to Alk^1 and R^3 aliphatic and heteroaliphatic chains.

Aromatic and heteroaromatic groups represented by R^{10} and R^{12} include those groups described hereinbefore for the group Ar^1. Optional substituents which may be present on these groups include those described in relation to R^3 aromatic and heteroaromatic groups.

When the group R^3 is an optionally substituted aromatic or heteroaromatic group it may be for example an aromatic or heteroaromatic group as described herein for the group Ar^1.

Optional substituents which may be present on the aromatic or heteroaromatic groups represented by the group R^3 include one, two, three or more substituents, each selected from an atom or group R^{13} in which R^{13} is $-R^{13a}$ or $-Alk^6(R^{13a})_m$, where R^{13a} is a halogen atom, or an amino ($-NH_2$), substituted amino, nitro, cyano, amidino, hydroxyl (-OH), substituted hydroxyl, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol (-SH), substituted thiol, $-COR^{14}$ [where R^{14} is an $-Alk^6(R^{13a})_m$, aryl or heteroaryl group], $-CSR^{14}$, $-SO_3H$, $-SOR^{14}$, $-SO_2R^{14}$, $-SO_3R^{14}$, $-SO_2NH_2$, $-SO_2NHR^{14}$ $SO_2N(R^{14})_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^{14}$, $-CSNHR^{14}$, $-CON[R^{14}]_2$, $-CSN(R^{14})_2$, $-N(R^{11})SO_2R^{14}$, $-N(SO_2R^{14})_2$, $-NH(R^{11})SO_2NH_2$, $-N(R^{11})SO_2NHR^{14}$, $-N(R^{11})SO_2N(R^{14})_2$, $-N(R^{11})COR^{14}$, $-N(R^{11})CONH_2$, $-N(R^{11})CONHR^{14}$, $-N(R^{11})CON(R^{14})_2$, $-N(R^{11})CSNH_2$, $-N(R^{11})CSNHR^{14}$, $-N(R^{11})CSN(R^{14})_2$, $-N(R^{11})CSR^{14}$, $-N(R^{11})C(O)OR^{14}$, $-SO_2NHet^1$ [where $-NHet^1$ is an optionally substituted C_{5-7}cyclicamino group optionally containing one or more other -O- or -S- atoms or $-N(R^{11})-$, -C(O)-, -C(S)-, S(O) or $-S(O)_2$ groups], $-CONHet^1$, $-CSNHet^1$, $-N(R^{11})SO_2NHet^1$, $-N(R^{11})CONHet^1$, $-N(R^{11})CSNHet^1$, $-SO_2N(R^{11})Het^2$ [where Het^2 is an optionally substituted monocyclic C_{5-7}carbocyclic group optionally containing one or more -O- or -S- atoms or $-N(R^{11})-$, -C(O)- or -C(S)- groups], $-Het^2$, $-CON(R^{11})Het^2$, $-CSN(R^{11})Het^2$, $-N(R^{11})CON(R^{11})Het^2$, $-N(R^{11})CSN(R^{11})Het^2$, cycloaliphatic, heterocyclo-aliphatic, aryl or heteroaryl group; Alk^6 is a straight or branched C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or $-S(O)_n$ [where n is an integer 1 or

2] or -N(R^{15})- groups [where R^{15} is a hydrogen atom or C_{1-6}alkyl, e.g. methyl or ethyl group]; and m is zero or an integer 1, 2 or 3. It will be appreciated that when two R^{11} or R^{14} groups are present in one of the above substituents, the R^{11} or R^{14} groups may be the same or different.

When in the group -Alk^6(R^{13a})$_m$ m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{13a} may be present on any suitable carbon atom in -Alk^6. Where more than one R^{13a} substituent is present these may be the same or different and may be present on the same or different atom in -Alk^6. Clearly, when m is zero and no substituent R^{13a} is present the alkylene, alkenylene or alkynylene chain represented by Alk^6 becomes an alkyl, alkenyl or alkynyl group.

When R^{13a} is a substituted amino group it may be for example a group -NHR^{14} [where R^{14} is as defined above] or a group -N(R^{14})$_2$ wherein each R^{14} group is the same or different.

When R^{13a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^{13a} is a substituted hydroxyl or substituted thiol group it may be for example a group -OR^{14} or a -SR^{14} or -SC(=NH)NH_2 group respectively.

Esterified carboxyl groups represented by the group R^{13a} include groups of formula -CO_2Alk^7 wherein Alk^7 is a group as defined hereinbefore.

When Alk^6 is present in or as a substituent it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, -S(O)$_2$- or -N(R^{15})- groups.

Cycloaliphatic or heterocycloaliphatic groups represented by the groups R^{13a} or R^{14} include those optionally substituted C_{3-10}cycloaliphatic or C_{3-10} heterocycloaliphatic groups described above for R^3.

Aryl or heteroaryl groups represented by the groups R^{13a} or R^{14} include mono- or bicyclic optionally substituted C_{6-12} aromatic or C_{1-9} heteroaromatic groups as described above for the group Ar^1. The aromatic and heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

When $-NHet^1$ or $-Het^2$ forms part of a substituent R^{13} each may be for example an optionally substituted pyrrolidinyl, pyrazolidinyl, piperazinyl, imidazolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, oxazolidinyl or thiazolidinyl group. Additionally Het^2 may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on $-NHet^1$ or $-Het^2$ include those substituents described above in relation to R^3 heterocycloaliphatic groups.

Particularly useful atoms or groups represented by R^{13} include fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thiazolyl, thienyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidinyl, dioxolanyl, dioxanyl, piperidinyl, oxazolidinyl, thiazolidinyl or imidazolidinyl, C_{1-6}hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC_{1-6}alkyl, e.g. carboxyethyl, C_{1-6}alkylthio e.g. methylthio or ethylthio, carboxyC_{1-6}alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C_{1-6}alkoxy, e.g. methoxy or ethoxy, hydroxyC_{1-6}alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C_{4-7}cycloalkyl, e.g. cyclobutyl, cyclopentyl, C_{5-7}cycloalkoxy, e.g. cyclopentyloxy, haloC_{1-6}alkyl, e.g. trifluoromethyl, haloC_{1-6}alkoxy, e.g. trifluoromethoxy, C_{1-6}alkylamino, e.g. methylamino, ethylamino or propylamino, amino ($-NH_2$), aminoC_{1-6}alkyl, e.g. aminomethyl or aminoethyl, C_{1-6}dialkylamino, e.g. dimethylamino or diethylamino, aminoC_{1-6}alkylamino e.g. aminoethylamino or aminopropyl-amino, optionally substituted Het^1NC_{1-6}alkylamino e.g. morpholinopropyl-amino, C_{1-6}alkylaminoC_{1-6}alkyl, e.g. ethylaminoethyl, C_{1-6}dialkyl-aminoC_{1-6}alkyl, e.g. diethylaminoethyl, aminoC_{1-6}alkoxy, e.g. aminoethoxy, C_{1-6}alkylaminoC_{1-6}alkoxy, e.g. methylaminoethoxy, C_{1-6}dialkylaminoC_{1-}

$_6$alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylamino-ethoxy, or dimethylaminopropoxy, hydroxyC_{1-6}alkylamino, e.g. hydroxyethylamino, hydroxypropylamino, or hydroxybutylamino, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl ($-CO_2H$), $-CO_2Alk^7$ [where Alk^7 is as defined above], C_{1-6} alkanoyl e.g. acetyl, propyryl or butyryl, optionally substituted benzoyl, thiol (-SH), thioC_{1-6}alkyl, e.g. thiomethyl or thioethyl, $-SC(=NH)NH_2$, sulphonyl ($-SO_3H$), $-SO_3Alk^7$, C_{1-6}alkylsulphinyl, e.g. methylsulphinyl, ethylsulphinyl or propylsulphinyl, C_{1-6}alkylsulphonyl, e.g. methylsulphonyl, ethylsulphonyl, or propyl-sulphonyl, optionally substituted C_{6-10}arylaminosulphonyl, e.g. phenyl-sulphonyl or dichlorophenylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6}alkylaminosulphonyl, e.g. methylaminosulphonyl, ethylaminosulphonyl or propylamiosulphonyl, C_{1-6}dialkylaminosulphonyl, e.g. dimethylamino-sulphonyl or diethylaminosulphonyl, optionally substituted phenylamino-sulphonyl, carboxamido ($-CONH_2$), C_{1-6}alkylaminocarbonyl, e.g. methyl-aminocarbonyl, ethylaminocarbonyl or propylaminocarbonyl, C_{1-6}dialkyl-aminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC_{1-6}alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C_{1-6}alkyl-aminoC_{1-6}alkylaminocarbonyl, e.g. methylaminoethylaminocarbonyl, C_{1-6}dialkylaminoC_{1-6}alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C_{1-6}alkylaminocarbonylamino, e.g. methylamino-carbonylamino or ethylaminocarbonylamino, C_{1-6}dialkylaminocarbonyl-amino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C_{1-6}alkylaminocabonylC_{1-6}alkylamino, e.g. methylaminocarbonylmethyl-amino, aminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C_{1-6}dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C_{1-6}alkylaminothiocarbonylC_{1-6}alkylamino, e.g. ethylaminothiocarbonylmethylamino, $-CONHC(=NH)NH_2$, C_{1-6}alkyl-sulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, haloC_{1-6}alkylsulphonylamino, e.g. trifluoromethylsulphonylamino, C_{1-6}dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonyl-amino, optionally substituted phenylsulphonylamino, aminosulphonylamino ($-NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, e.g. methylaminosulphonyl-amino or ethylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, .g.

dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonylC_{1-6}alkylamino, optionally substituted phenylaminosulphonylamino, C_{1-6}alkanoylamino, e.g. acetylamino, aminoC_{1-6}alkanoylamino e.g. aminoacetylamino, C_{1-6}dialkylaminoC_{1-6}alkanoylamino, e.g. dimethylaminoacetylamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, e.g. acetylaminomethyl, C_{1-6}alkanoylaminoC_{1-6}alkylamino, e.g. acetamidoethylamino, C_{1-6}alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or optionally substituted benzyloxy, benzylamino, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxycarbonylaminoC_{1-6}alkyl e.g. benzyloxycarbonylaminoethyl, thiobenzyl, pyridylmethylthio or thiazolylmethylthio groups.

Where desired, two R^{13} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6}alkylenedioxy group such as methylenedioxy or ethylenedioxy.

It will be appreciated that where two or more R^{13} substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the aromatic or heteroaromatic group represented by R^3.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

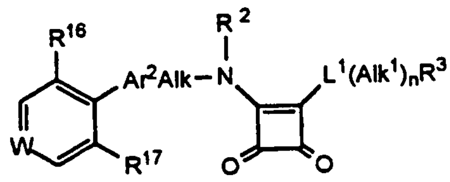
Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

In the compounds according to the invention the group R^1 is preferably an Ar^1Ar^2Alk- group in which Ar^1 is an optionally substituted phenyl, monocyclic heteroaromatic or bicyclic heteroaromatic group. Particularly useful monocyclic heteroaromatic groups are optionally substituted five- or six-membered heteroaromatic groups as described previously, especially five- or six-membered heteroaromatic groups containing one or two heteroatoms selected from oxygen, sulphur or nitrogen atoms. Nitrogen-containing groups are especially useful, particularly pyridyl or pyrimidinyl groups. Particularly useful substituents present on these Ar^1 groups include halogen atoms or alkyl, haloalkyl, $-OR^5$, $-SR^5$, $-NR^5R^6$, $-CO_2H$, $-CO_2R^5$, $-NO_2$, $-SOR^5$, $-SO_2R^5$, $-N(R^5)SO_2R^6$, $-SO_2N(R^5)(R^6)$, $-N(R^5)COR^6$, $-N(R^5)CON(R^6)(R^7)$, $-CONR^5R^6$, $-CON(R^5)SO_2R^6$ or -CN groups as described above in relation to the compounds of formula (1). Particularly useful bicyclic heteraromatic groups represented by Ar^1 include optionally substituted ten-membered fused-ring heteroaromatic groups containing one or two heteroatoms, especially nitrogen atoms. Particular examples include optionally substituted naphthyridinyl, especially 2,6-naphthyridinyl, quinolinyl and isoquinolinyl, especially isoquinolin-1-yl groups. Particular optional substituents include those just described for monocyclic heteroaromatic groups.

A particularly useful group of compounds according to the invention has the formula (2a):

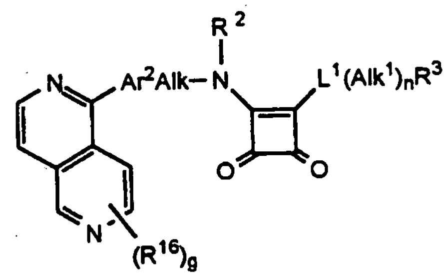


(2a)

wherein -W= is -CH= or -N=;
R^{16} and R^{17}, which may be the same or different is each a hydrogen atom or an atom or group $-L^2(Alk^2)_tL^3(R^4)_u$ in which L^2, Alk^2, t, L^3, R^4 and u are as defined previously;
L^1, Ar^2, Alk, R^2, Alk^1, n and R^3 are as defined for formula (1);
and the salts, solvates, hydrates and N-oxides thereof.

R^{16} and R^{17} in compounds of formula (2a) is each preferably as particularly described above for compounds of formula (1), other than a hydrogen atom. Particularly useful R^{16} and R^{17} substituents include halogen atoms, especially fluorine or chlorine atoms, or methyl, halomethyl, especially $-CF_3$, $-CHF_2$ or $-CH_2F$, methoxy or halomethoxy, especially $-OCF_3$, $-OCHF_2$ or $-OCH_2F$ groups.

A further particularly useful group of compounds according to the invention has the formula (2b):



(2b)

wherein R^{16}, L^1, Ar^2, Alk, R^2, Alk^1, n and R^3 are as defined for formula (2a);
g is the integer 1,2,3 or 4;
and the salts, solvates, hydrates and N-oxides thereof.

Each R^{16} atom or group in compounds of formula (2b) may be independently selected from an atom or group $-L^2(Alk^3)_tL^3(R^7)_u$ in which L^2, Alk^2, t, L^3, R^4 and u are as previously defined. Particularly useful R^{16} substituents when present in compounds of formula (2b) include halogen atoms, especially fluorine, chlorine or bromine atoms, or methyl, halomethyl, especially $-CF_3$, methoxy or halomethoxy, especially $-OCF_3$, -CN, $-CO_2CH_3$, $-NO_2$, amino ($-NH_2$), substituted amino ($-NR^5R^6$) and $-N(R^5)COCH_3$, especially $-NHCOCH_3$ groups.

In general Alk in compounds of the invention is preferably:

$$\underset{\displaystyle CH_2R}{\overset{}{-\underset{|}{C}H-}} \quad \text{or, especially,} \quad -CH_2CH(R)-.$$

In general in compounds of formulae (1), (2a) and (2b) R^2 is preferably a hydrogen atom.

In one preferred group of compounds of formulae (1), (2a) and (2b) R is a $-CO_2H$ group.

In another preferred group of compounds of formulae (1), (2a) and (2b) R is an esterified carboxyl group of formula $-CO_2Alk^7$. In this group of compounds Alk^7 is preferably an optionally substituted C_{1-8}alkyl group, especially a methyl, ethyl, propyl or i-propyl group, a C_{6-10}aryl group, especially a phenyl group, an optionally substituted C_{6-10}arylC_{1-6}alkyl group, especially a benzyl group, a C_{3-8}heterocycloalkylC_{1-6}alkyl group, especially a morpholinyl-N-ethyl group or a C_{1-6}alkyloxyC_{1-6}alkyl group, especially a methyloxyethyl group. Especially preferred esterfied carboxyl groups include $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$ and $-CO_2CH(CH_3)_2$ groups.

The group Ar^2 in compounds of formulae (1), (2a) and (2b) is preferably an optionally substituted phenylene group. Particularly useful groups include optionally substituted 1,4-phenylene groups.

In general in compounds of formulae (1), (2a) and (2b) when n is zero or the integer 1 the group R^3 may especially be a hydrogen atom or an optionally substituted heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group as defined herein. Particularly useful groups of this type include optionally substituted C_{2-6}heteroalkyl, particularly C_{1-3}alkoxyC_{1-3}alkyl, especially methoxypropyl, optionally substituted C_{3-7}cycloalkyl, especially optionally substituted cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, optionally substituted C_{5-7}heterocycloaliphatic, especially optionally substituted pyrrolidinyl, thiazolidinyl, pyrolidinonyl, piperidinyl, morpholinyl or piperazinyl, optionally substituted C_{6-12}aromatic especially optionally substituted phenyl and optionally substituted C_{5-7}heteroaromatic, especially optionally substituted pyridyl, triazinyl or imidazolyl groups. Optional substituents on these groups include in particular R^{13} atoms or groups where R^3 is an aromatic or heteroaromatic group. Particularly useful R^{13} atoms or groups include a halogen atom, especially fluorine or chlorine and C_{1-6}alkoxy, especially methoxy.

Where R^3 is a nitrogen-containing heterocycloaliphatic group such as a pyrrolidinyl, thiazolidinyl, pyrrolidinonyl, piperidinyl, homopiperidinyl, heptamethyleneiminyl, morpholiny, piperazinyl or homopiperazinyl group optional substituents include in particular $-(L^5)_p(Alk^5)_qR^{12}$ groups as described earlier.

In one preferred group of compounds of formulae (1), (2a) and (2b) L^1 is present as a $-N(R^8)-$ group. Particularly useful $-N(R^8)-$ groups include -NH-, $-N(CH_3)-$, $-N(CH_2CH_3)-$ and $-N(CH_2CH_2CH_3)-$ groups. In this class of compounds n is preferably the integer 1 and Alk^1 is preferably an optionally substituted straight or branched C_{1-6}alkylene chain. Particularly useful Alk^1 chains include $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$ and $-C(CH_3)CH_2-$. R^3 in this group of compounds is preferably a hydrogen atom.

In another pr f rred group of compounds of formulae (1), (2a) and (2b) Alk^1 is present as an aliphatic chain as defined herein (i.e. n is the integer 1) and R^3 is a hydrogen atom. In this class of compounds L^1 is preferably

a covalent bond. Compounds of this type where Alk^1R^3 is a C_{1-6}alkyl group, particularly a methyl, ethyl, propyl, butyl, isopropyl, t-butyl or C_{1-6}alkenyl group particularly an allyl group are especially useful. A most especially useful Alk^1R^3 group is a $-C(CH_3)_3$ group.

In another preferred group of compounds of formulae (1), (2a) and (2b), L^1 is a covalent bond, n is zero and R^3 is an optionally substituted C_{5-7}heterocycloaliphatic group. Especially useful C_{5-7}heterocycloaliphatic groups include optionally substituted piperidinyl, homopiperidinyl, heptamethyleneiminyl, pyrrolidinyl, piperazinyl, homopiperazinyl, morpholinyl and thiomorpholinyl groups. Most preferred C_{5-7}heterocycloaliphatic groups are those linked via a ring nitrogen atom to the remainder of the compound of formulae (1), (2a) or (2b). Most especially useful C_{5-7} heterocycloaliphatic groups include optionally substituted pyrolidin-1-yl, piperidin-1-yl and homopiperidin-1-yl groups. Especially useful optional substituents on these C_{5-7}heterocycloaliphatic groups include optionally substituted C_{1-6}alkyl groups, especially methyl, ethyl and i-propyl groups. Most preferred optionally substitued C_{5-7}heterocycloaliphatic groups include 2-methylpyrrolidin-1-yl, cis and trans 2,5-dimethylpyrrolidin-1-yl, 2-methylpiperidin-1-yl, cis and trans 2,6-dimethylpiperidin-1-yl, homopiperidin-1-yl, 2-methylhomopiperidin-1-yl and cis and trans 2,7-dimethylhomopiperidin-1-yl groups.

Particularly useful compounds of the invention include:
(2*S*)-3-(4-[2',6'-dimethoxy]biphenylyl)-2-{(2-[1-propylamino]-3,4-dioxo-cyclobut-1-enyl)amino}propanoic acid;
(2*S*-)3-(4-[2',6'-dimethoxy]biphenylyl)-2-{(2-[diethylamino]-3,4-dioxo-cyclobut-1-enyl)amino}propanoic acid;
and the salts, solvates, hydrates, N-oxides and carboxylic acid esters, particularly the methyl, ethyl, propyl and i-propyl esters thereof.

Compounds according to the invention are potent and selective inhibitors of α4 integrins and have advantageous clearance properties, especially those compounds where R is a carboxylic ester or amide. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

The compounds are of use in modulating cell adhesion and in particular are of use in the prophylaxis and treatment of diseases or disorders involving inflammation in which the extravasation of leukocytes plays a role and the invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such diseases or disorders.

Diseases or disorders of this type include inflammatory arthritis such as rheumatoid arthritis vasculitis or polydermatomyositis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses such as psoriasis or dermatitis, asthma and inflammatory bowel disease.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be pr sent d as a dry product for constitution with water or other suitable vehicle befor us . Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable

additives such as susp nding agents, emulsifying agents, non-aqu ous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

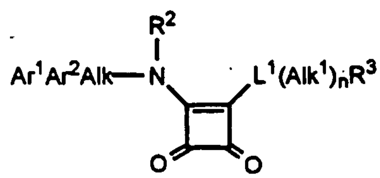
For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichloro-fluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may b accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols Ar^1, Ar^2, Alk, R^1, R^2, R^3, L^1, L^2, Alk^1 and n when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991 and the Examples hereinafter]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups. For convenience the processes described below all refer to a preparation of a compound of formula (1) but clearly the description applies equally to the preparation of compounds of formula (2).

Thus according to a further aspect of the invention, a compound of formula (1) in which R is a $-CO_2H$ group may be obtained by hydrolysis of an ester of formula (3):



(3)

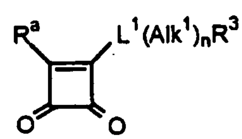
where Alk represents a group $-CH_2CH(CO_2R^y)-$, $-CH=CH(CO_2R^y)-$, or

$$-\underset{\displaystyle CH_2CO_2R^y}{\underset{|}{CH}}-$$

[where R^y is an alkyl group for example a C_{1-6}alkyl group]

The hydrolysis may be performed using either an acid or a base depending on the nature of R^y, for example an organic acid such as trifluoroacetic acid or an inorganic base such as lithium, sodium or potassium hydroxide optionally in an aqueous organic solvent such as an amide e.g. a substituted amide such as dimethylformamide, an ether e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol e.g. methanol at a temperature from ambient to the reflux temperature. Where desired, mixtures of such solvents may be used.

According to a further aspect of the invention a compound of formula (3) may be prepared by displacement of a leaving group from a compound of formula (4):

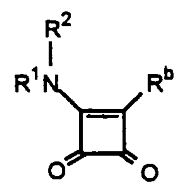


(4)

where R^a is a leaving group, with an amine R^1R^2NH or a salt thereof. Suitable leaving groups represented by R^a include halogen atoms, especially chlorine and bromine atoms, or alkoxy, e.g. methoxy, ethoxy or isopropoxy, aryloxy, e.g. dinitrophenyloxy, or aralkoxy, e.g. benzyloxy, groups.

The reaction may be performed in an inert solvent or mixture of solvents, for example a substituted amide such as dimethylformamide, an alcohol such as methanol or ethanol and/or a halogenated hydrocarbon such as dichloromethane, at a temperature from 0°C to the reflux temperature. Where necessary, for example when a salt of an amine R^1R^2NH is used, an organic base such as diisopropylethylamine can be added.

It will be appreciated that the displacement reaction may also be performed on a compound of formula (5):

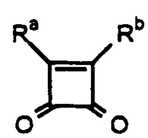


(5)

where R^b is a leaving group as defined for R^a using an intermediate $R^3(Alk^1)_nL^1H$ where $-L^1H$ is a functional group such as an amine ($-NH_2$) using the reaction conditions just described.

Where desired the displacement reaction may also be performed on an intermediate of formulae (4) or (5), R^1R^2NH or $R^3(Alk^2)_nL^1H$ which is linked, for example via its R^1 or R^3 group, to a solid support, such as a polystyrene resin. After the reaction the desired compound of formula (1) may be displaced from the support by any convenient method, depending on the original linkage chosen. Particular examples of such solid phase synetheses are given in the Examples hereinafter.

Intermediates of formulae (4) and (5) are either readily available or may be prepared from an intermediate of formula (6):



(6)

where R^a and R^b are as previously defined and an amine R^1R^2NH, $R^3(Alk^1)_nL^1H$ where L^1H is a functional group such as an amine ($-NH_2$) or alcohol (-OH), alkyllithium or aryllithium by displacement as just described for the preparation of compounds of formula (1).

Intermediates of formulae R^1R^2NH and $R^3(Alk^1)_nL^1H$ may be obtained from simpler, known compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other compounds of formulae (1), (2a), (2b) and (3) where appropriate functional groups exist in these compounds.

Thus compounds of the invention and intermediates thereto may be prepared by alkylation, arylation or heteroarylation. For example intermediates of formula R^1R^2NH may be obtained from reaction or intermediates of formula $XAr^2AlkN(R^2)H$ [where X is a halogen atom such as bromine or iodine or a sulphonate such as trifluoromethylsulphonate] with a boronic acid $Ar^1B(OH)_2$, optionally in the presence of a base such as a carbonate e.g. sodium or potassium carbonate or an amine e.g. triethylamine or pyridine iand a metal complex such as a palladium complex e.g. tetrakis(triphenylphosphine)palladium (0) in a solvent such as an aromatic hydrocarbarbon e.g. toluene or an ether e.g. 1,2-dimethyoxyethane or tetrahydrofuran in the presence of water at an elevated temperature e.g. 80°.

In the reaction as just described for the synthesis of intermediates of formula R^1R^2NH boronic acids of formula $Ar^1B(OH)_2$ may be replaced by organometallic reagents such as organostannanes of formula $Ar^1Sn(R^z)_3$ (where R^z is a C_{1-6}alkyl group), Grignard reagents of formula Ar^1MgHal (where Hal is a halogen atom such as a chlorine, bromine or iodine atom) or organozinc reagents of formula Ar^1ZnHal. In any reaction involving such reagents water is omitted from the reaction conditions as just described,

Intermediates of formula $XAr^2AlkN(R^2)H$ [where X is a sulphonate] may be obtained from intermediates of formula $XAr^2AlkN(R^2)H$ [where X is a hydroxyl (-OH) group| by reaction with an anhydride such as a sulphonic anhydride e.g. trifluoromethanesulphonic anhydride in the presence of a base such as an amine e.g. triethylamine or pyridine in a solvent such as a halogenated hydrocarbon e.g. dichloromethane, at for example 0^oC.

In another example, compounds containing a $-L^1H$ or $-L^2H$ group (where L^1 and L^2 is each a linker atom or group) may be treated with an alkylating agent $R^3(Alk^1)_nX^1$ or $R^4L^3(Alk^2)_tX^1$ respectively in which X^1 is a leaving atom or group such as a halogen atom, e.g. a fluorine, bromine, iodine or chlorine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

The reaction may be carried out in the presence of a base such as a carbonate, e.g. cesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, or an organic amine e.g. triethylamine or N,N-diisopropylethylamine or a cyclic amine, such as N-methylmorpholine or pyridine, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

In another example, compounds containing a $-L^1H$ or $-L^2H$ or group as defined above may be functionalised by acylation or thioacylation, for example by reaction with one of the alkylating agents just described but in which X^1 is replaced by a $-C(O)X^2$, $C(S)X^2$, $-N(R^8)COX^2$or $-N(R^8)C(S)X^2$ group in which X^2 is a leaving atom or group as described for X^1. The reaction may be performed in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature. Alternatively, the acylation may b carried out under the same conditions with an acid (for example one of the alkylating agents described above in which X^1 is replaced by a $-CO_2H$ group) in the presence of a condensing agent, for

example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, or a benzotriazole such as [0-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium]hexafluorophosphate advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to the desired acylation reaction

In a further example compounds may be obtained by sulphonylation of a compound containing an -OH group by reaction with one of the above alkylating agents but in which X^1 is replaced by a -S(O)Hal or $-SO_2Hal$ group [in which Hal is a halogen atom such as chlorine atom] in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

In another example, compounds containing a $-L^1H$ or $-L^2H$ group as defined above may be coupled with one of the alkylation agents just described but in which X^1 is replaced by an -OH group in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate.

In a further example, ester groups $-CO_2R^5$, $-CO_2Alk^3$ or $-CO_2Alk^7$ in the compounds may be converted to the corresponding acid [$-CO_2H$] by acid- or base-catalysed hydrolysis depending on the nature of the groups R^5, Alk^3 or Alk^7. Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

In a further example, $-OR^5$ or $-OR^{14}$ groups [where R^5 or R^{14} each represents an alkyl group such as methyl group] in compounds of formula (1) may be cleaved to the corresponding alcohol -OH by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C.

Alcohol [-OH] groups may also be obtained by hydrogenation of a corresponding $-OCH_2R^{14}$ group (where R^{14} is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [CO_2Alk^5 or CO_2R^5] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

In another example, alcohol -OH groups in the compounds may be converted to a corresponding $-OR^5$ or $-OR^{14}$ group by coupling with a reagent R^5OH or $R^{14}OH$ in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

Aminosulphonylamino [$-NHSO_2NHR^3$] groups in the compounds may be obtained, in another example, by reaction of a corresponding amine [$-NH_2$] with a sulphamide $R^3NHSO_2NH_2$ in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In another example compounds containing a $-NHCSR^3$ or $-CSNHR^3$ group may be prepared by treating a corrsponding compound containing a $-NHCOR^3$ or $-CONHR^3$ group with a thiation reagent, such as Lawesson's Reagent, in an anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, at an elevated temperature such as the reflux temperature.

In a further example amine ($-NH_2$) groups may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxyborohyride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in th presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine [$-NH_2$] groups in compounds of formula (1) may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [$-NO_2$] group may be reduced to an amine [$-NH_2$], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

In another example, sulphur atoms in the compounds, for example when present in a linker group L^1 or L^2 may be oxidised to the corresponding sulphoxide or sulphone using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient t mperature.

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

The following Examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

NMM - N-methylmorpholine;	EtOAc - ethyl acetate;
MeOH - methanol;	BOC - butoxycarbonyl;
DCM - dichloromethane;	AcOH - acetic acid;
DIPEA - diisopropylethylamine;	EtOH - ethanol;
Pyr - pyridine;	Ar - aryl;
DMSO - dimethylsulphoxide;	iPr - isopropyl;
Et_2O - diethyleth r;	Me - methyl;
THF - tetrahydrofuran;	DMF - N,N-dimethylformamid ;

FMOC - 9-fluorenylmethoxycarbonyl; DME - 1,2-dimethoxyethane; aq. - aqueous;

All NMR's were obtained at 300MHz unless otherwise indicated.

INTERMEDIATE 1

Methyl (2S)-3-(4-biphenylyl)-2-[(2-isopropoxy-3,4-dioxocyclobut-1-enyl)amino]propanoate

A mixture of methyl (2*S*)-2-amino-3-(4-biphenylyl)-propanoate hydrochloride (415mg, 1142mmol),3,4-diisopropoxy-3-cyclobutene-1,2-dione (281mg, 1.42mmol), DIPEA (247μl, 1.42mmol) and MeOH (10ml) was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2; DCM/MeOH, 98:2) to give the title compound (358mg). δH (DMSO-d^6, 390K) 8.50 (1H, d, J 8.0Hz), 7.63-7.56 (4H, m), 7.47-7.42 (2H, m), 7.36-7.32 (3H, m), 5.24-5.18 (1H, m), 4.80-4.75 (1H, m), 3.74 (3H, s), 3.31 (1H, dd, J 14.2, 5.2Hz), 3.13 (1H, dd, J 14.2, 9.4Hz), 1.38 (3H, d, J 6.0Hz), 1.37 (3H, d, J 6.1Hz); m/z (ES^+, 70V) 394 (MH^+).

INTERMEDIATE 2

Methyl (2S)-2-[(*tert*-butoxycarbonyl)amino]-3-(4-{[trifluoromethylsulphonyl]oxy}phenyl)propanoate

Triflic anhydride (5.05ml, 30mmol) was added to a mixture of N-BOC tyrosine methyl ester (7.38g, 25mmol) and pyridine (10ml, 125mmol) in DCM (40ml) at 0^o. After 45min at 0^o water (80ml) and DCM (100ml) were added. The organic phase was washed with NaOH aq. (0.5M, 60ml), water (60ml), citric acid (10%, 2 x 80ml) and water (60ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as a yellow oil which solidified on standing (10.6g). δH ($CDCl_3$) 7.26-7.18 (4H, m), 5.05 (1H, v br d), 4.59 (1H, v br q), 3.70 (3H, s), 3.16 (1H, dd, J 13.7, 5.7Hz), 3.02 (1H, dd, J 13.8, 6.5Hz), 1.40 (9H, s); m/z (ES^+, 70V) 450 (M^++ Na).

INTERMEDIATE 3

Methyl (2S)-2-[(*tert*-butoxycarbonyl)amino]-3-(4-[2',6'-dimethoxy] biphenylyl)propanoate

A mixture of the Intermediate 2 (4.27g, 10mmol), 2,6-dimethoxybenzene boronic acid (4.55g, 25mmol), potassium carbonate (6.9g, 50mmol)

tetrakis(triphenylphosphine)palladium(0) (2.31g) in DME (45ml) and water (5ml) was heated at 80^o overnight. The mixture was diluted with EtOAc, washed with dilute HCl, $NaHCO_3$ (aq.), water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography (SiO_2; EtOAc/hexane, 20:80 - 30:70) gave the title compound (2.27g). δH (DMSO-d^6) 7.33 (1H, d, J 8.2Hz), 7.27 (1H, t, J 8.3Hz), 7.20 (2H, d, J 8.1Hz), 7.10 (2H, d, J 8.0Hz), 6.71 (2H, d, J 8.4Hz), 4.2 (1H, m), 3.63 (9H, s), 3.01 (1H, dd, J 13.9, 4.5Hz), 2.84 (1H, dd, J 13.7, 10.3Hz), 1.34 (9H, s); m/z (ES$^+$, 70V) 438 (M$^+$ + Na).

INTERMEDIATE 4

Methyl (2S)-2-amino-3-(4-[2',6'-dimethoxy]biphenylyl)propanoate hydochloride

Anhydrous HCl was bubbled through a solution of Intermediate 3 (1.30g, 3.13mmol) in EtOAc (30ml) for a few seconds. The mixture was stirred at room temperture for 1h. Some solvent was removed *in vacuo* until material began to precipitate. The precipitate was filtered off and dried to give the title compound as pale yellow crystals (888mg, 81%). δH (DMSO-d^6) 8.7 (2H, br s), 7.28 (1H, t, J 8.4Hz), 7.21 (2H, d, J 8.4Hz), 7.17 (2H, d, J 8.3Hz), 6.73 (2H, d, J 8.4Hz), 4.30 (1H, t, J 6.6Hz), 3.69 (3H, s), 3.64 (6H, s), 3.18 (1H, dd, J 14.1, 6.2Hz), 3.10 (1H, dd, J 14.1, 7.1Hz); m/z (ES$^+$, 70V) 316 (MH$^+$).

INTERMEDIATE 5

Methyl (2S)-3-(4-[2',6'-dimethoxy]biphenylyl)-2-[(2-isopropoxy-3,4-dioxo-cyclobut-1-enyl)amino]propanoate

A mixture of Intermediate 4 (325mg, 1.0mmol) 3,4-diisopropoxy-3-cyclobutene-1,2-dione (208mg, 1.05mmol), NMM (115μl, 1.05mmol) and MeOH (10ml) was heated at reflux overnight. The solvent was removed *in vacuo*. The residue was dissolved in DCM, washed with dilute HCl, dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography (SiO_2; MeOH/DCM, 3:97) gave the title compound as a yellow gum (425mg). δH (DMSO-d^6, 390K), 8.50 (1H, br d, J 8.5Hz), 7.26 (1H, t, J 8.3Hz), 7.22 (2H, d, J 8.3Hz), 7.16 (2H, d, J 8.4Hz), 6.73 (2H, d, J 8.3Hz), 5.22 (1H, sept, J 6.2Hz), 4.81-4.75 (1H, br m), 3.74 (3H, s), 3.65 (6H, s), 3.29 (1H, dd, J

14.2, 5.1Hz), 3.10 (1H, dd, J 14.2, 9.6Hz), 1.39 (3H, d, J 6.3Hz), 1.38 (3H, d, J 6.2Hz); m/z (ES$^+$, 70V) 454 (MH$^+$).

INTERMEDIATE 6

Methyl (2*S*)-2-[(tert-butoxycarbonyl)amino]-3-(4-[2'-methoxy] biphenylyl)propanoate

The title compound (944mg) was prepared from Intermediate 2 (2.14g, 5mmol) and 2-methoxybenzeneboronic acid (1.52g, 10mmol) by a similar method to that used to prepare Intermediate 3. δH (DMSO-d^6) 7.67-7.23 (6H, m), 7.10-6.97 (3H, m), 4.20 (1H, m), 3.74 (3H, s), 3.63 (3H, s), 3.02 (1H, dd, J 13.7, 4.9Hz), 2.85 (1H, dd, J 14.0, 10.2Hz), 1.33 (9H, s); m/z (ES$^+$, 70V) 408 (M$^+$+ Na).

INTERMEDIATE 7

Methyl (2*S*)-2-amino-3-(4-[2'-methoxy]biphenylyl)propanoate hydrochloride

The title compound was obtained from Intermediate 6 by the method used to prepare Intermediate 4. δH (DMSO-d^6) 8.68 (2H, br s), 7.44 (2H, d, J 8.2Hz), 7.36-7.24 (2H, m), 7.26 (2H, d, J 8.4Hz), 7.10 (1H, d, J 7.6Hz), 7.02 (1H, dt, J 7.4, 1.0Hz), 4.30 (1H, t, J 6.5Hz), 3.75 (3H, s), 3.71 (3H, s), 3.23-3.10 (2H, m); m/z (ES$^+$, 70V) 286 (MH$^+$).

INTERMEDIATE 8

Methyl (2*S*)-3-(4-[2'-methoxy]biphenylyl)-2-([2-isopropoxy-3,4-dioxo-cyclobut-1-enyl]amino)propanoate

The title compound was obtained from Intermediate 7 by the method used to prepare Intermediate 5. δH (DMSO-d^6, 390K) 8.48 (1H, br d, J 8.6Hz), 7.41 (2H, d, J 8.3Hz), 7.34-7.25 (4H, m), 7.10 (1H, dd, J 8.3, 1.0Hz), 7.02 (1H, dt, J 7.4, 1.1Hz), 5.21 (1H, sept, J 6.2Hz), 4.80-4.75 (1H, m), 3.76 (3H, s), 3.75 (3H, s), 3.31 (1H, dd, J 14.2, 5.1Hz), 3.12 (1H, dd, J 14.3, 9.5Hz), 1.39 (3H, d, J 6.2Hz), 1.38 (3H, d, J 6.1Hz); m/z (ES$^+$, 70V) 424 (MH$^+$).

INTERMEDIATE 9

3-(Diethylamino)-4-isopropoxy-3-cyclobutene-1,2-dione

A mixture of 3,4-diisopropoxy-3-cyclobutene-1,2-dione (1.0g, 5.05mmol) and diethylamine (549µl, 5.30mmol) in EtOH (25ml) was stirred overnight at room temperature. The solvent was removed *in vacuo* to give the title compound as a yellow oil (1.0g). δH (DMSO-d^6, 390K) 5.33-5.27 (1H, m), 3.58 (4H, q, J 7.1Hz), 1.42 (6H, d, J 6.1Hz), 1.23 (6H, t, J 7.2Hz); m/z (ES$^+$, 70V) 212 (MH$^+$).

INTERMEDIATE 10

Methyl (R)-3-[(tert-butoxycarbonyl)amino]-3-(4-hydroxyphenyl)] propionate

Methyl 3-[(amino)(4-hydroxyphenyl)]propionate [Davies S. G. and Ichihara, O. Tet. Asym 2, 3, 183-186 (1991)] (870mg, 4.5mmol) was dissolved in dioxan (5ml) and aqueous sodium hydrogen carbonate solution (5ml). di-tert-butrylcarbonate (877mg) in dioxan (2ml) was added and the reaction stirred at room temperature for 16h. Water was added and the solution extracted into EtOAc (x 3), dried over Na_2SO_4, filtered and concentrated to give the crude product. Column chromatography (silica; DCM/MeOH 20:1) gave the title compound (900mg, 68%) as a white solid. δH (DMSO-d^6, 300K) 9.27 (1H, s), 7.09 (2H, d, J 8.5Hz), 6.68 (2H, d, J 8.5Hz), 4.82 (1H, m), 3.54 (3H,s), 2.70 (1H, dd, J 15.2, 8.7Hz), 2.61 (1H, dd, J 15.2, 6.5Hz) and 1.35 (9H, s); m/z (ES$^+$, 70V) 318 (M+Na).

INTERMEDIATE 11

Methyl (R)-3-[(tert-butoxycarbonyl)amino]-3-(4-trifluoromethyl-sulphonyloxyphenyl)]propionate

Intermediate 10 (450mg, 1.53mmol) in DCM (5ml) and pyridine (0.62ml) was cooled to 0° and trifluoromethylsulphonylanhydride (0.24ml) added. The solution was stirred at 0° for 30min then quenched with saturated $NaHCO_3$ solution, washed with water, dried over Na_2SO_4, filtered and concentrated to give the title compound (430mg, 66%) as a colourless oil. δH (DMSO-d^6, 400MHz), 7.40-7.20 (4H, m), 4.98 (1H, br m), 3.56 (3H, s), 2.85 (2H, m) and 1.35 (9H, s). m/z (ES$^+$, 70V) 450 (M+Na).

INTERMEDIATE 12

Methyl (R)-3-[(tert-butoxycarbonyl)amino]-3-(4-[2',6'-dimethoxy] biphenylyl)propionate

Intermediate 11 (430mg, 1mmol) was dissolved in DMF (3ml) and triethylamine (0.28ml), 2,6-dimethoxybenzeneboronic acid (367mg), tetrakis(triphenylphosphine) palladium (O) (146mg) added and the mixture heated at 120° for 1h. The mixture was cooled, concentrated, dissolved into EtOAc, wash with water (x 3), brine, dried (Na_2SO_4), filtered and concentrated. Column chromatograpy (SiO_2; DCM/MeOH 50:1) gave the title compound (270mg, 63%) as a pale brown solid. δH (DMSO-d^6) 7.30 (5H, m), 6.65 (2H, d, J 8.4Hz), 5.30 (1H, br m), 5.18 (1H, br m), 3.72 (6H, s), 3.66 (3H, s), 2.89 (2H, m), 1.44 (9H, s); m/z (ES$^+$, 70V) 438 (M+Na).

INTERMEDIATE 13

Methyl (R)-3-amino-3-(4-[2',6'-dimethoxy]biphenylyl)propionate

Intermediate 12 (270mg) in EtOAc (5ml) was treated with excess HCl gas then stirred for 30min. The precipitate was filtered to give the title compound (211mg, 95%) as a pale brown solid. δH (DMSO-d^6) 8.73 (2H, br m), 7.50 (2H, d, J 8.2Hz), 7.30 (1H, t, J 8.4Hz), 7.25 (2H, d, J 8.2Hz), 6.74 (2H, d, J 8.4Hz), 4.60 (1H, t, J 7.8Hz), 3.65 (6H, s), 3.60 (3H,s), 3.23 (1H, dd, J 16.5, 6.3Hz) and 3.04 (1H, dd, J 16.5, 8.1Hz); m/z (ES$^+$, 70V) 299 (M-NH_3).

INTERMEDIATE 14

Derivatised Resin (1)

Resin bound (S)-3-(4-Iodophenyl)-2-(2-([-propylamino]-3,4-dioxocyclobut-1-enylamino)propanoic acid (1)

Wang resin (Advanced ChemTech, 5.0g, 0.70mmol/g, 3.50mmol equivalent) in a mixture of DMF (20ml) and DCM (20ml) was treated with N-α-FMOC-4-Iodo-L-phenylalanine (4.51g, 8.75mmol), 1,3-diisopropyl-carbodiimide (1.40ml, 8.75mmol) and 4-N,N-dimethylaminopyridine (0.43g, 0.35mmol) and the mixture was agitated at room temperature for 16h. The resin was filtered and washed with DMF, DCM and MeOH, then air-dried. The resin was treated with a 20% solution of acetic anhydride in DMF for 30mins at room temperature, then filtered and washed as before. The resulting resin was treated with a 20% solution of piperidine in DMF (50ml) for 30mins at room temperature, then filtered and washed with DMF, DCM and MeOH. The resin was r -suspended in DMF (50ml) and was treated with 3,4-dimethoxy-3-cyclobut ne-1,2-dione (2.50g, 17.50mmol) and the

mixture agitated at room temperature for 16h. The resin was filtered and washed with DMF, DCM and MEOH, then re-suspended in a mixture of DCM (200m) and MeOH (50ml) and treated with 1-propylamine (2.90ml, 35.00mmol). The reaction mixture was agitated at room temperature for 4h. The resin was filtered and washed with DMF, DCM and MeOH, then air-dried to give the title derivatised resin (1).

EXAMPLE 1

Methyl (2S)-3-(4-biphenylyl-2-{(2-[1-propylamino]-3,4-dioxo-cyclobut-1-enyl)amino}propanoate

n-Propylamine (104μl, 1.26mmol) was added to a solution of Intermediate 1 (412mg, 1.05mmol) in MeOH (10ml). The mixture was stirred at room temperature overnight then the solvent removed *in vacuo*. The residue was dissolved in DCM (100ml), washed with HCl (aqueous) (1M, 30ml), dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound as a yellow solid (337mg). δH (DMSO-d^6, 390K) 7.69 (1H, br), 7.65-7.59 (4H, m), 7.55 (1H, br), 7.47-7.44 (2H, m), 7.37-7.33 (1H, m), 7.26 (2H, d, J 7.5Hz), 5.06 (1H, br), 3.73 (3H, s), 3.45 (2H, br), 3.24 (1H, br),3.73 (3H, s), 3.45 (2H, br), 3.24 (1H, dd, J 14.2, 5.2Hz), 3.12 (1H, dd, J 13.8, 7.7Hz), 1.55-1.48 (2H, m), 0.87 (3H, t, J 7.3Hz).

EXAMPLE 2

(2S)-3-(4-Biphenylyl)-2-{(2-[1-propylamino]-3,4-dioxo-cyclobut-1-enyl)amino}propanoic acid

Lithium hydroxide monohydrate (1.03mmol, 43mg) was added to the compound of Example 1 (337mg, 0.86mmol) in THF (10ml) and water (10ml). The mixture was stirred at room temperature overnight. The THF was removed *in vacuo* and the aqueous residue acidified to pH1-2 with HCl (1M). The precipitate was filtered off, washed with water and ether and dried to give the title compound as a brown solid (191mg). δH (DMSO-d^6, 390K) 7.64-7.59 (2H, m), 7.55-7.52 (2H, m,), 7.47-7.46 (2H, m), 7.45-7.31 (3H, m), 7.50-7.20 (2H, br), 5.13-5.11 (1H, br), 3.54-3.46 (2H, m), 3.32 (1H, dd, J 14.0, 5.3Hz), 3.18 (1H, dd, J 14.0, 7.1Hz),1.59-1.53 (2H, m), 0.92 (3H, t, J 7.4Hz); m/z (ES$^+$, 70V) 379 (MH$^+$).

EXAMPLE 3

Methyl (2S)-3-(4-[2',6'-dimeth xy]biphenylyl)-2-{(2-[1-propylamino]-3,4-dioxo-cyclobut-1-enyl)amino}propanoate

The title compound (327mg, 78%) was prepared from Intermediate 5 (420,g. 0.93mmol) by the method used to prepared the compound of Example 1. δH (DMSO-d^6, 390K), 7.27 (1H, t, *J* 8.3Hz), 7.18 (4H, s), 6.74 (2H, d, *J* 8.3Hz), 7.35-7.10 (2H, br), 5.08 (1H, m), 3.73 (3H, s), 3.65 (6H, s), 3.49-3.47 (2H, m), 3.24 (1H, dd, *J* 14.2, 5.9Hz), 3.14 (1H, dd, *J* 14.2, 7.8Hz), 1.63-1.55 (2H, m), 0.93 (3H, t, *J* 7.4Hz); *m/z* (ES^+, 70V) 453 (MH^+).

EXAMPLE 4

(2S)-3-(4-[2',6'-dimethoxy]biphenylyl)-2-{(2-[1-propylamino]-3,4-dioxo-cyclobut-1-enyl)amino}propanoic acid

The *title compound* was prepared from the compound of Example 3 by a similar method to that used to prepare the compound of Example 2. δH (DMSO-d^6, 390K) 7.26 (1H, t, *J* 8.3Hz), 7.21 (2H, d, *J* 8.3Hz), 7.16 (2H, d, *J* 8.4Hz), 6.74 (2H, d, *J* 8.3Hz), 7.35-7.20 (2H, br), 4.99 (1H, br m), 3.65 (6H, s), 3.51-3.47 (2H, m), 3.26 (1H, dd, *J* 14.2, 5.6Hz), 3.11 (1H, dd, *J* 14.2, 7.5Hz), 1.63-1.54 (2H, m), 0.93 (3H, t, *J* 7.4Hz); *m/z* (ES^+, 70V) 439 (MH^+).

EXAMPLE 5

Methyl (2S-3-(4-[2',6'-dimethoxy]biphenylyl)-2-{(2-[diethylamino]-3,4-dioxo-cyclobut-1-enyl)amino}propanoate

Diethylamine (84µl, 0.82mmol) was added to a solution of Intermediate 5 (185mg, 0.408mmol) in MeOH (5ml). The mixture was heated at 50° for 3h. The solvent was removed *in vacuo*. The residue was purified by column chromatography (SiO_2;MeOH/DCM, 2:98) to give the *title compound* as a colourless gum (164mg, 86%). δH (DMSO-d^6) 7.77 (1H, d, *J* 8.9Hz), 7.26 (1H, t, *J* 8.3Hz), 7.22 (2H, d, *J* 8.3Hz), 7.10 (2H, d, *J* 8.2Hz), 6.70 (2H, d, *J* 8.4Hz), 5.23-5.15 (1H, m), 3.71 (3H, s), 3.61 (6H, s), 3.51 (4H, br m), 3.30-3.20 ($C\underline{H}_AH_BAr$, under HOD signal), 3.06 (1H, dd, *J* 13.9, 10.9Hz), 1.08 (6H, t, *J* 7.1Hz); *m/z* (ES^+, 70V) 467 (MH^+).

EXAMPLE 6

(2S-)3-(4-[2',6'-dimethoxy]biphenylyl)-2-{(2-[diethylamino]-3,4-dioxo-cyclobut-1-enyl)amino}propanoic acid

The title compound was prepared from the compound of Example 5 by a similar method to that used to prepare the compound of Example 2. δH (DMSO-d^6, 390K) 7.39-7.30 (3H, m), 7.22 (2H, d, J 8.3Hz), 7.01 (1H, br d, J 7.3Hz), 6.79 (2H, d, J 8.0Hz), 5.27-5.23 (1H, m), 3.70 (6H, s), 3.68-3.52 (3H, m), 3.38 (1H, dd, J 14.3, 5.1Hz), 3.21 (1H, dd, J 14.2, 9.1Hz), 1.22 (6H, t, J 7.1Hz); m/z (ES$^+$, 70V) 453 (MH$^+$).

EXAMPLE 7

Methyl (2S)-3-(4-[2'-methoxy]biphenylyl)-2-{(2-[diethylamino]-3,4-dioxo-cyclobut-1-enyl)amino}propanoate

The title compound was obtained from intermediate 8 by the method used to prepare the compound of Example 5. δH (DMSO-d^6) 7.77 (1H, d, J 9.0Hz), 7.37 (2H, d, J 8.2Hz), 7.34-7.21 (2H, m), 7.27 (2H, d, J 8.1Hz), 7.08 (1H, d, J 7.6Hz), 6.99 (1H, t, J 7.4Hz), 5.18 (1H, m), 3.72 (3H, s), 3.71 (3H, s), 3.50 (4H), ~3.30 (1H), 3.07 (1H, dd, J 13.9, 10.8Hz), 1.07 (6H, t, J 7.1Hz), m/z (ES$^+$, 70V) 437 (MH$^+$).

EXAMPLE 8

(2S)-3-(4-[2'-Methoxy]biphenylyl)-2-{(2-[diethylamino]-3,4-dioxo-cyclobut-1-enyl)amino}propanoic acid

The title compound was obtained from the compound of Example 7 by the method used to prepare the compound of Example 2. δH (DMSO-d^6, 390K) 7.40 (2H, d, J 8.4Hz), 7.33-7.25 (2H, m), 7.30 (2H, d, J 8.3Hz), 7.09 (1H, dd, J 8.2, 1.0Hz), 7.02 (1H, dt, J 7.4, 1.1Hz), 6.95 (1H, br d), 5.21-5.17 (1H, m), 3.75 (3H, s), 3.58-3.52 (4H, m), 3.32 (1H, dd, J 14.2, 5.2Hz), 3.17 (1H, dd, J 14.2, 9.2Hz), 1.16 (6H, t, J 7.1Hz); m/z (ES$^+$, 70V) 423 (MH$^+$).

EXAMPLE 9

Methyl (2S)-3-(4-[2'-methoxy]biphenylyl)-2-{(2-[1-propylamino]-3,4-dioxo-cyclobut-1-enyl)amino}propanoate

The title compound was obtained from Intermediate 8 by the method used to prepare the compound of Example 3. δH (DMSO-d^6, 390K) 7.42 (2H, d, J 8.3Hz), 7.34-7.24 (2H, m), 7.30 (2H, br), 7.23 (2H, d, J 8.2Hz), 7.10

(1H, dd, J 8.2, 0.9Hz), 7.02 (1H, dt, J 7.4,1.1Hz), 5.08 (1H, t, J 6.7Hz), 3.76 (3H, s), 3.74 (3H, s), 3.49 (2H, t, J 6.8Hz), 3.26 (1H, dd, J 14.1, 5.8Hz), 3.14 (1H, dd, J 14.1, 7.7Hz), 1.59 (2H, sext, J 7.1Hz), 0.93 (3H, t, J 7.4Hz), m/z (ES^+, 70V) 423 (MH^+).

EXAMPLE 10

(2S)-3-(4-[2'-Methoxy]biphenylyl)-2-{(2-[1-propylamino]-3,4-dioxo-cyclobut-1-enyl)amino}propanoic acid

The title compound was obtained from the compound of Example 9 by the method used to prepare the compound of Example 2. δH (DMSO-d^6, 390K) 7.41 (2H, d, J 8.3Hz), 7.34-7.23 (6H, m, ArH), 7.10 (1H, dd, J 8.2, 1.0Hz), 7.02 (1H, dt, J 7.4, 1.1Hz, 5.01-4.98 (1H, m), 3.76 (3H, s), 3.49 (1H, br t, J 6.7Hz), 3.27 (1H, dd, J 14.2, 5.6Hz), 3.13 (1H, dd, J 14.2, 7.5Hz), 1.58 (2H, sext, J 7.2Hz), 0.93 (3H, t, J 7.4Hz); m/z (ES^+, 70V) 409 (MH^+).

EXAMPLE 11

Methyl (2S)-3-(4-biphenylyl)-2-{(2-[diethylamino]-3,4-dioxo-cyclobut-1-enyl)amino}propanoate

A mixture of (2*S*)-2-amino-3-[4-biphenylyl)propanoate hydrochloride (437mg, 1.5mmol), Intermediate 9 (275mg, 1.5mmol) and DIPEA (261μl, 1.5mmol) in MeOH (10ml) was stirred at room temperature overnight. The solvent was removed *in vacuo*. The residue was dissolved in DCM, washed with dilute HCl, dried (Na_2SO_4) and concentrated *in vacuo*. Crystallisation (EtOAc) gave the title compound as yellow crystals (308mg). δH (DMSO-d^6, 390K) 7.61-7.58 (2H, m), 7.56-7.44 (2H, m), 7.42-7.40 (2H, m), 7.35-7.30 (3H, m), 7.10 (1H, d, J 8.7Hz), 5.29-5.24 (1H, m), 3.73 (3H, s), 3.57-3.56 (4H, m), 3.32 (1H, dd, J 14.2, 5.4Hz), 3.17 (1H, dd, J 14.2, 9.2Hz), 1.14 (6H, t, J 7.1Hz); m/z (ES^+, 70V) 407 (MH^+).

EXAMPLE 12

(2S)-3-(4-Biphenylyl)-2-{(2-[diethylamino]-3,4-dioxo-cyclobut-1-enyl)amino}propanoic acid

The title compound was obtained from the compound of Example 11 by the method used to prepare the compound of Example 2. δH (DMSO-d^6, 390K) 7.52-7.49 (2H, m), 7.46-7.43 (2H, m), 7.35-7.31 (2H, m), 7.27-7.21

(3H, m), 5.10-5.07 (1H, m), 3.47-3.39 (4H, m), 3.22 (1H, dd, J 14.2, 5.2Hz), 3.07 (1H, dd, J 14.2, 9.1Hz), 1.05 (6H, t, J 7.1Hz); m/z (ES+, 70V) 393 (MH^+).

EXAMPLE 13

Methyl (R)-3-[4-(2',6'-dimethoxy)biphenylyl]-3-[(2-isopropoxy-3,4-dioxo-cyclobut-1-enyl)amino]propionate

Intermediate 13 (211mg, 0.6mmol) in MeOH (3ml) was treated with DIPEA (0.23ml) and 3,4-diisopropoxy-3-cyclobutene-1,2-dione (130mg) at room temperature for 16h. The mixture was concentrated then purified by column chromatography (silica; DCM/MeOH 50:1) gave the title compound (196mg, 72%) as a pale yellow oil. δH (DMSO-d^6) 9.34 (1H, m), 7.29 (3H, m), 7.19 (2H, d, J 7.9Hz), 6.71 (2H, d, J 8.4Hz), 5.74 (1H, m), 5.24 (1H, m), 3.64 (6H, m), 3.92 (3H, s), 3.0 (2H, m), 1.35 (6H, m). m/z (ES^+, 70V) 454 (MH^+).

EXAMPLE 14

Methyl (R)-3-{[2-(diethylamino)-3,4-dioxo-cyclobut-1-enyl]-3-[4-(2',6'dimethoxy)biphenylyl] propionate

The compound of Example 13 (190mg, 0.42mmol) in MeOH (4ml) was treated with diethylamine (0.065ml) and stirred at room temperature for 1h. The precipitate was filtered and dried to give the title compound (169mg, 87%) as a white solid. δH (DMSO-d^6) 7.37 (2H, d, J 8.2Hz), 7.28 (1H, t, J 8.3Hz), 7.18 (2H, d, J 8.2Hz), 6.71 (2H, d, J 8.3Hz), 5.90 (1H, m), 3.64 (3H, s), 3.60 (3H, s), 3.50 (4H, m), 3.30 (3H, s), 3.00 (2H, m) and 1.23 (6H, t, J 7.1Hz); m/z (ES^+, 70V) 467 (MH^+).

EXAMPLE 15

(*R*)-3-{[2-(Diethylamino)-3,4-dioxo-cycylobut-1-enyl]amino-3-[4-(2',6'-dimethoxy)biphenylyl]propionic acid

The compound of Example 14 in THF (2ml) and H_2O (2ml) was treated with lithium hydroxide (22mg) and stirred at room temperatue for 2h. The THF was removed *in vacuo* and the remaining solution acidified with dilute HCl solution to give a white precipitate which was filtered and dried to give th title compound (99mg, 63%). δH (DMSO-d^6, 400K) 7.42 (2h, d, J 8.1Hz), 7.25 (3H, m), 6.75 (2H, d, J 8.1Hz), 5.92 (1H, m), 3.68 (6H, s),

3.60 (2H, q, J 7.1Hz), 3.58 (2H, q, J 7.1Hz), 3.04 (1H, dd, J 15.7, 8.3Hz), 2.95 (1H, dd, J 15.7, 5.9Hz) and 1.21 (6H, t, J 7.1Hz); m/z (ES$^+$, 70V) 453 (MH$^+$).

EXAMPLE 16

(2S)-3-(4-Biphenylyl)-2-[(2-morpholino-3,4-dioxocyclobut-1-enyl)amino] propanoic acid

N-α-FMOC-L-4-biphenylylalanine Wang resin (Advanced ChemTech, 200mg, 0.50mmol/g, 0.1mmol equivalent) was treated with a 20% solution of piperidine in DMF (2ml) for 30min at room temperature, then filtered and washed with DCM. The resin was re-suspended in DMF (2ml) and treated with 3,4-dimethoxy-3-cyclobutene-1,2-dione (99mg, 0.7mmol). The resulting mixture was heated at 70° for 18h. The resin was filtered and washed with DCM then re-suspended in a mixture of DCM (0.4ml) and ethanol (1.6ml) and treated with morpholine (87mg, 1.0mmol). The resin was agitated at room temperature for 18h then filtered and washed with DCM. The resin was treated with a solution of trifluoroacetic acid/DCM (95:5, 2ml) for 3h, then filtered. The filtrate was evaporated to afford the crude product which was purified by preparative HPLC to afford the title compound (4mg).

HPLC-MS Retention time 2.44min 407 (MH$^+$).

EXAMPLE 17

(2S)-3-[4-(4'-Methoxy)biphenylyl]-2-{(2-[propylamino)]3,4-dioxocyclobut-1-enyl)amino}propanoic acid

A slurry of derivatised resin (1) (200mg) in anhydrous, degassed DMF (2ml) was treated with 4-methylbenzeneboronic acid (49mg, 0.35mmol), triethylamine (0.1ml, 0.67mmol) and tetrakistriphenylphosphine palladium (0) (20mg, 0.17mmol). The resulting mixture was agitated at 100° for 2h then cooled to room temperature. The resin was filtered and washed with 0.5% (w/w) sodium diethydithiocarbamate solution in DMF, 0.5% (w/w) DIPEA solution in DMF, DMF, DCM and MeOH then air-dried. The resin was treated with a solution of trifluoroacetic acid/DMF (95:5, 1ml) for 1h, then filtered. The filtrate was evaporated to afford the title compound (1mg).

HPLC-MS Retention time 2.62min 393 (MH$^+$).

LC-MS Conditions : Luna C18(2) 50 x 2.0mm (3um) column, running a gradient of 95% [0.1% aqueous formic acid], 5% [0.1% formic acid in acetonitrile] to 10% [0.1% aqueous formic acid], 90% [0.1% formic acid in acetonitrile] over 2min, then maintaining the mobile phase at that ratio for a further 1min. Flow rate 0.8ml/min. MS was acquired by API electrospray in positive ion mode, at 70V, scanning from 120 to 750amu.

The compounds of Examples 18 to 23 were prepared from derivatised resin (1) in a similar manner to the compound of Example 17, using the arylboronic acid shown.

EXAMPLE 18

(2S)-3-[4-(2'-(Trifluoromethyl)biphenylyl]-2-{(2-(1-propylamino]-3,4-dioxo-cyclobut-1-enyl)amino}propanoic acid

2-(Trifluoromethyl)benzeneboronic acid gave the title compound (1mg)
HPLC-MS Retention time 2.62min 447 (MH^+).

EXAMPLE 19

(sS)-3-[4-(2'-Formyl)biphenylyl]-2-{(2-(1-propylamino]-3,4-dioxo-cyclobut-1-enyl)amino}propanoic acid

2-Formylbenzeneboronic acid gave the title compound (2mg)
HPLC-MS Retention time 2.45min 407 (MH^+).

EXAMPLE 20

(2S)-3-[4-(2',5' -Dimethoxy)biphenylyl]-2-(2-(1-propylamino)-3,4-dioxocyclobut-1-enylamino)propanoic acid

2,5-Dimethoxybenzeneboronic acid gave the title compound (2mg)
HPLC-MS Retention time 2.53min 439 (MH^+).

EXAMPLE 21

(2S)-3-[4-(2'-Formyl-5'-methoxy)biphenylyl]-2-(2-(1-propylamino)-3,4-dioxocyclobut-1-enylamino)propanoic acid

2-Formyl-5-methoxybenzeneboronic acid gave the title compound (5mg)
HPLC-MS Retention time 2.46min 437 (MH^+).

EXAMPLE 22

(2S)-3-[4-(5'-Chloro-2'-methoxy)biphenylyl]-2-{(2-(1-propylamino]-3,4-dioxo-cyclobut-1-enyl)amino}propanoic acid

5-Chloro-2-methoxybenzeneboronic acid gave the title compound (3mg) HPLC-MS Retention time 2.64min 443 (MH^+).

EXAMPLE 23

(2S)-3-[4-(5'-Formyl-2'-methoxy)biphenylyl]-2-(2-(1-propylamino)-3,4-dioxocyclobut-1-enylamino)propanoic acid

5-Formyl-2-methoxybenzeneboronic acid gave the title compound (5mg) HPLC-MS Retention time 2.42min 437 (MH^+).

The following assays can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each of these assays an IC_{50} value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition of cell adhesion where 100% = adhesion assessed in the absence of the test compound and 0% = absorbance in wells that did not receive cells.

$\alpha_4\beta_1$ Integrin-dependent Jurkat cell adhesion to VCAM-Ig

96 well NUNC plates were coated with $F(ab)_2$ fragment goat anti-human IgG Fcγ-specific antibody [Jackson Immuno Research 109-006-098: 100 μl at 2 μg/ml in 0.1M $NaHCO_3$, pH 8.4], overnight at 4°. The plates were washed (3x) in phosphate-buffered saline (PBS) and then blocked for 1h in PBS/1% BSA at room temperature on a rocking platform. After washing (3x in PBS) 9 ng/ml of purified 2d VCAM-Ig diluted in PBS/1% BSA was added and the plates left for 60 minutes at room temperature on a rocking platform. The plates were washed (3x in PBS) and the assay then performed at 37° for 30 min in a total volume of 200 μl containing 2.5×10^5 Jurkat cells in the presence or absence of titrated test compounds.

Each plate was washed (2x) with medium and the adherent cells were fixed with 100μl methanol for 10 minutes followed by another wash. 100μl 0.25% Rose Bengal (Sigma R4507) in PBS was added for 5 minutes at room temperature and the plates washed (3x) in PBS. 100μl 50% (v/v)

ethanol in PBS was add d and the plates left for 60min after which the absorbance (570nm) was measured.

$\alpha_4\beta_7$ Integrin-dependent JY cell adhesion to MAdCAM-Ig

This assay was performed in the same manner as the $\alpha_4\beta_1$ assay except that MAdCAM-Ig (150ng/ml) was used in place of 2d VCAM-Ig and a sub-line of the β-lympho blastoid cell-line JY was used in place of Jurkat cells. The IC_{50} value for each test compound was determined as described in the $\alpha_4\beta_1$ integrin assay.

$\alpha_5\beta_1$ Integrin-dependent K562 cell adhesion to fibronectin

96 well tissue culture plates were coated with human plasma fibronectin (Sigma F0895) at 5µg/ml in phosphate-buffered saline (PBS) for 2 hr at 37°C. The plates were washed (3x in PBS) and then blocked for 1h in 100µl PBS/1% BSA at room temperature on a rocking platform. The blocked plates were washed (3x in PBS) and the assay then performed at 37°C in a total volume of 200µl containing 2.5x 10^5 K562 cells, phorbol-12-myristate-13-acetate at 10ng/ml, and in the presence or absence of titrated test compounds. Incubation time was 30 minutes. Each plate was fixed and stained as described in the $\alpha_4\beta_1$ assay above.

$\alpha_m\beta_2$-dependent human polymorphonuclear neutrophils adhesion to plastic

96 well tissue culture plates were coated with RPMI 1640/10% FCS for 2h at 37°C. 2 x 10^5 freshly isolated human venous polymorphonuclear neutrophils (PMN) were added to the wells in a total volume of 200µl in the presence of 10ng/ml phorbol-12-myristate-13-acetate, and in the presence or absence of test compounds, and incubated for 20min at 37°C followed by 30min at room temperature. The plates were washed in medium and 100µl 0.1% (w/v) HMB (hexadecyl trimethyl ammonium bromide, Sigma H5882) in 0.05M potassium phosphate buffer, pH 6.0 added to each well. The plates were then left on a rocker at room temperature for 60 min. Endogenous peroxidase activity was then assessed using tetramethyl benzidine (TMB) as follows: PMN lysate samples mixed with 0.22% H_2O_2 (Sigma) and 50µg/ml TMB (Boehringer Mannheim) in 0.1M sodium acetate/citrate buffer, pH 6.0 and absorbance measured at 630nm.

<u>$\alpha IIb/\beta_3$ -dependent human platelet aggregation</u>

Human platelet aggregation was assessed using impedance aggregation on the Chronolog Whole Blood Lumiaggregometer. Human platelet-rich plasma (PRP) was obtained by spinning fresh human venous blood anticoagulated with 0.38% (v/v) tri-sodium citrate at 220xg for 10 min and diluted to a cell density of 6 x 10^8/ml in autologous plasma. Cuvettes contained equal volumes of PRP and filtered Tyrode's buffer (g/liter: NaCl 8.0; $MgCl_2.H_2O$ 0.427; $CaCl_2$ 0.2; KCl 0.2; D-glucose 1.0; $NaHCO_3$ 1.0; $NaHPO_4.2H_2O$ 0.065). Aggregation was monitored following addition of 2.5μM ADP (Sigma) in the presence or absence of inhibitors.

In the above assays the preferred compounds of the invention in which R^1 is an α_4 integrin binding group, such as the compounds of the Examples generally have IC_{50} values in the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ assays of 1 μM and below. In the other assays featuring α integrins of other subgroups the same compounds had IC_{50} values of 50μM and above thus demonstrating the potency and selectivity of their action against α_4 integrins.

The advantageous clearance properties of compounds according to the invention may be demonstrated as follows:

Hepatic clearance, whether metabolic or biliary, can make a substantial contribution to the total plasma clearance of a drug. The total plasma clearance is a principal parameter of the pharmacokinetic properties of a medicine. It has a direct impact on the dose required to achieve effective plama concentrations and has a major impact on the elimination half-life and therefore the dose-interval. Furthermore, high hepatic clearance is an indicator of high first-pass hepatic clearance after oral administration and therefore low oral bioavailability.

Many peptidic and non-peptidic carboxylic acids of therapeutic interest are subject to high hepatic clearance from plasma. Except for drugs which function in the liver, hepatic uptake from blood or plasma is undesirable b cause it l ads to high hepatic clearance if the compound is excreted in

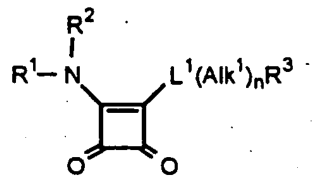
bile or metabolised, or if the substance is not cleared from the liv r, it may accumulate in the liver and interfere with the normal function of the liver.

The total plasma clearance of a compound according to the invention can be determined as follows:
a small dose of the compound in solution is injected into a vein of a test animal. Blood samples are withdrawn from a blood vessel of the animal at several times after the injection, and the concentration of compound in the bleed or plasma is measured using a suitable assay. The area under the curve (AUCiv) is calculated by non-compartmental methods (for example, the trapezium method) or by pharmacokinetic modelling. The total plasma clearance (CL_p) is calculated by dividing the *intravenous* dose(D_{iv}) by the AUC_{iv} for the blood plasma concentration - time course of a drug administered by the *intravenous* route: $CL_p = D_{iv} \div AUC_{iv}$

When tested in this manner, compounds according to the invention are not rapidly or extensively extracted by the liver and have low total plasma clearance where low is defined as less than 10 ml/min/kg in the laboratory rat (Sprague Dawley CD). This compares favourably with functionally equivalent integrin binding compounds in which the square acid framework and/or the carboxylic ester or amide R group of compounds of formula (1) is not present.

CLAIMS

1. A compound of formula (1):



(1)

wherein
R^1 is a group Ar^1Ar^2Alk- in which:
Ar^1 is an optionally substituted aromatic or heteroaromatic group;
Ar^2 is an optionally substituted phenylene or nitrogen-containing six-membered heteroarylene group; and Alk is a chain

$-CH_2-CH(R)-$, $-CH=C(R)-$, $\begin{array}{c}-CH-\\ |\\ CH_2R\end{array}$

in which R is a carboxylic acid ($-CO_2H$) or a derivative or biostere thereof;
R^2 is a hydrogen atom or a C_{1-6}alkyl group;
L^1 is a covalent bond or a linker atom or group;
n is zero or the integer 1;
Alk^1 is an optionally substituted aliphatic chain;
R^3 is a hydrogen atom or an optionally substituted heteroaliphatic, cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, heteropolycycloaliphatic, aromatic or heteroaromatic group:
and the salts, solvates, hydrates and N-oxides thereof.

2. A compound according to Claim 1 in which Alk is a chain

$-CH_2-CH(R)-$ or $\begin{array}{c}-CH-\\ |\\ CH_2R\end{array}$

3. A compound according to Claim 1 or Claim 2 in which R is a carboxylic acid ($-CO_2H$) group.

4. A compound according to Claim 1 or Claim 2 in which R is an esterifed carboxyl group of formula $-CO_2Alk^7$.

5. A compound according to any one of Claims 1 to 4 in which Ar^2 is an optionally substituted phenylene group.

6. A compound according to any one of Claims 1 to 5 in which Ar^1 is an optionally substituted phenyl, or five-, six- or ten-membered heteroaromatic group.

7. A compound according to Claim 6 in which Ar^1 is an optionally substituted pyridyl, pyrimidinyl, naphthyridinyl, quinolinyl or isoquinolinyl group.

8. A compound according to any one of Claims 1 to 7 in which L^1 is a $-N(R^8)-$ group where R^8 is a hydrogen atom or an optionally substituted C_{1-6}alkyl group.

9. A compound according to Claim 8 in which R^8 is a methyl, ethyl or n-propyl group.

10. A compound according to any one of Claims 1 to 7 in which L^1 is a covalent bond.

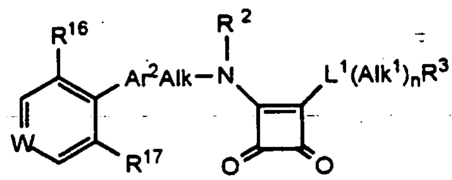
11. A compound according to any one of Claims 1 to 10 in which n is the integer 1 and Alk^1 is an optionally substituted straight or branched C_{1-6}alkylene chain and R^3 is a hydrogen atom.

12. A compound according to Claim 11 in which Alk^1 is a $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$ or $-C(CH_3)_2CH_2-$ chain.

13. A compound according to any one of Claims 1 to 7 in which L^1 is a covalent bond, n is zero and R^3 is an optionally substituted C_{5-7}heterocycloaliphatic group.

14. A compound according to Claim 13 in which R^3 is an optionally substituted piperidinyl, homopiperidinyl, heptamethyleneiminyl, pyrrolidinyl, piperazinyl, homopiprazinyl, morpholinyl or thiomorpholinyl group.

15. A compound according to Claim 1 of formula (2a):

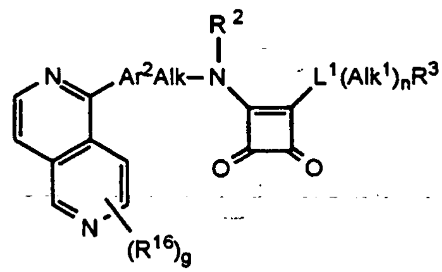


(2a)

wherein -W= is -CH= or -N=;
R^{16} and R^{17}, which may be the same or different is each a hydrogen atom or an atom or group $-L^2(Alk^2)_tL^3(R^4)_u$ in which ;
L^2 is a covalent bond or a linker atom or group;
Alk^2 is an aliphatic or heteroaliphatic chain;
t is zero or the integer 1;
L^3 is a covalent bond or a linker atom or group;
u is the integer 1, 2 or 3;
R^4 is a hydrogen or halogen atom or a group selected from optionally substituted C_{1-6}alkyl or C_{3-8}cycloalkyl, -Het, [where Het is an optionally substituted monocyclic C_{5-7}carbocyclic group optionally containing one or more -O- or -S- atoms or $-N(R^5)-$ (where R^5 is a hydrogen atom or an optionally substitued C_{1-6}alkyl or C_{3-8}cycloalkyl group), -C(O)- or -C(S)- groups], $-OR^5$ $-SR^5$, $-NR^5R^6$ [where R^6 is as just defined for R^5 and may be the same or different], $-NO_2$, -CN, $-CO_2R^5$, $-SO_3H$, $-SOR^5$, $-SO_2R^5$, $-SO_3R^5$, $-OCO_2R^5$, $-CONR^5R^6$, $-OCONR^5R^6$, $-CSNR^5R^6$, $-COR^5$, $-OCOR^5$, $-N(R^5)COR^6$, $-N(R^5)CSR^6$, $-SO_2N(R^5)(R^6)$, $-N(R^5)SO_2R^6$, $-CON(R^5)SO_2R^6$, $-N(R^5)CON(R^6)(R^7)$ [where R^7 is a hydrogen atom or an optionally substituted C_{1-6}alkyl or C_{3-8}cycloalkyl group], $-N(R^5)CSN(R^6)(R^7)$ or $-N(R^5)SO_2N(R^6)(R^7)$, provided that when t is zero and each of L^2

and L^3 is a covalent bond then u is the integer 1 and R^4 is other than a hydrogen atom
and the salts, solvates, hydrates and N-oxides thereof.

16. A compound according to Claim 1 of formula (2b):



(2b)

wherein R^{16} is a hydrogen atom or a group $-L^2(Alk^2)_tL^3(R^4)_u$ in which;
L^2 is a covalent bond or a linker atom or group;
Alk^2 is an aliphatic or heteroaliphatic chain;
t is zero or the integer 1;
L^3 is a covalent bond or a linker atom or group;
u is the integer 1, 2 or 3;
g is the integer 1, 2, 3 or 4;
R^4 is a hydrogen or halogen atom or a group selected from optionally substituted C_{1-6}alkyl or C_{3-8}cycloalkyl, -Het, [where Het is an optionally substituted monocyclic C_{5-7}carbocyclic group optionally containing one or more -O- or -S- atoms or $-N(R^5)-$ (where R^5 is a hydrogen atom or an optionally substitued C_{1-6}alkyl or C_{3-8}cycloalkyl group), -C(O)- or -C(S)- groups], $-OR^5$ $-SR^5$, $-NR^5R^6$ [where R^6 is as just defined for R^5 and may be the same or different], $-NO_2$, -CN, $-CO_2R^5$, $-SO_3H$, $-SOR^5$, $-SO_2R^5$, $-SO_3R^5$, $-OCO_2R^5$, $-CONR^5R^6$, $-OCONR^5R^6$, $-CSNR^5R^6$, $-COR^5$, $-OCOR^5$, $-N(R^5)COR^6$, $-N(R^5)CSR^6$, $-SO_2N(R^5)(R^6)$, $-N(R^5)SO_2R^6$, $-CON(R^5)SO_2R^6$, $-N(R^5)CON(R^6)(R^7)$ [where R^7 is a hydrogen atom or an optionally substituted C_{1-6}alkyl or C_{3-8}cycloalkyl group], $-N(R^5)CSN(R^6)(R^7)$ or $-N(R^5)SO_2N(R^6)(R^7)$, provided that when t is zero and each of L^2

and L^3 is a covalent bond then u is the integer 1 and R^4 is other than a hydrogen atom
and the salts, solvates, hydrates and N-oxides thereof.

17. A compound which is:
(2*S*)-3-(4-[2',6'-dimethoxy]biphenylyl)-2-{(2-[1-propylamino]-3,4-dioxo-cyclobut-1-enyl)amino}propanoic acid;
(2*S*-)3-(4-[2',6'-dimethoxy]biphenylyl)-2-{(2-[diethylamino]-3,4-dioxo-cyclobut-1-enyl)amino}propanoic acid;
and the salts, solvates, hydrates, N-oxides and carboxylic acid esters, particularly the methyl, ethyl, propyl and i-propyl esters thereof.

18. A pharmaceutical composition comprising a compound according to Claim 1 together with one or more pharmaceutically acceptable carriers, excipients or diluents.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/GB 00/04995

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C225/20 C07C229/46 C07D295/12 A61K31/13 A61K31/435
A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 18460 A (DUGGAN MARK E ;MERCK & CO INC (US); HARTMAN GEORGE D (US)) 7 May 1998 (1998-05-07) the whole document	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 February 2001	20/02/2001

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/04995

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9818460 A	07-05-1998	AU 722360 B	03-08-2000
		AU 5239998 A	22-05-1998
		EP 0946165 A	06-10-1999
		US 5952341 A	14-09-1999